Analysis of Multiple Control Strategies for Pre-Exposure Prophylaxis and Post-infection Interventions on HIV Infection

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This dissertation is submitted in fulfilment of the academic requirements for the degree of Doctor of Philosophy in Applied Mathematics to the School of Mathematics, Statistics and Computer Science; College of Agriculture, Engineering and Science, University of KwaZulu-Natal, Durban.

As the candidate's supervisors, we have approved this dissertation for submission.

Dr. Faraimunashe Chirove ..... December 15, 2016.

Prof. Keshlan Govinder..... December 15, 2016.

Abstract

HIV pre-exposure prophylaxis (PrEP) of which advocates the use of antiretroviral (ARV) agents by uninfected individuals at high risk infection, has recently become a promising preventive measure against sexual HIV transmission. While results from clinical trials undertaken in different parts of the world hold the promise that PrEP intervention could significantly stem the risk of new sexual HIV transmission, very little attention has so far been given to the analysis of the impact of PrEP strategy in mathematical modelling to explore the processes that inform the current trends and other possible feedback mechanisms that can not be captured by the clinical trials. In this research study, we develop mathematical HIV models to investigate the impact of PrEP use as a single intervention and PrEP intervention in combination with other strategies such as ARV therapy (ART) and post-infection educational support services, on HIV incidence and prevalence. Thus, throughout the models analysis, PrEP awareness level, PrEP efficacy level, and ARV treatment rate are considered as key aspects of HIV control. PrEP drug resistance is also considered in our model analysis to examine its contribution to the HIV infection spread. PrEP as a control strategy, is first considered as a single intervention to examine different PrEP intervention scenarios where PrEP use and PrEP efficacy are implemented at high/low levels. Results obtained suggest that the strategy with high PrEP use and high PrEP efficacy level significantly reduces HIV incidence, compared to the other strategies considered, but may not continuously keep the HIV burden under check. ART intervention is thus incorporated into the PrEP model to assess the benefit of combining both strategies in reducing new infections, compared with PrEP intervention alone. The results show that strategies with PrEP and ART interventions offer the best benefits in new HIV infections reduction when efficacy and adherence to PrEP and ART are maintained at high levels. The results also

show that the contribution of PrEP drug resistance into the spread of HIV infection would partially depend on the duration of inadvertent PrEP use by the already-infected individuals. Results obtained from the PrEP intervention in combination with post-infection education for risky behavioural change demonstrate that with time dependent controls (optimal controls), the cumulative number of new HIV infections would be effectively reduced in a very short time.

Declaration

I declare that the contents of this dissertation are original except where due reference has been made. It has not been submitted before for any degree to any other institution.

Komi Afassinou

Declaration 1 - Plagiarism

I, Komi Afassinou, declare that

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3. This thesis does not contain other persons data, pictures, graphs or other information, unless specifically acknowledged as being sourced from other persons.

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Signed .....

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Contents

Chapter 1

Introduction

In the 1980s, when the Centers for Disease Control and Prevention (CDC) brought the world attention to the Acquired Immunodeficiency Syndrome (AIDS) disease, which later was revealed to be caused by the Human Immunodeficiency Virus (HIV), the scientific committee and healthcare authorities optimistically believed that an effective vaccine or a cure would soon be developed to effectively treat the reported ill patients so as to avoid an outbreak. However, more than three decades later, neither a vaccine nor successful treatment proposed could stop the transmission or effectively cure those carrying the virus. Alternative preventive/treatment approaches have been developed and used to slow down the rapid progression of HIV infection, but more than a million of people get infected and thousands die from the disease every year. The global endemicity level of HIV infection remains alarming in every part of the world, and there is a need to continuously conduct research and investigate of new strategies that could systematically eradicate the HIV pandemic. Results from some recent studies suggested new effective approaches, which were demonstrated potently effective in preventing new HIV infections. The potent and the most promising approach, currently under investigation, is the use of antiretroviral drugs by uninfected individuals at high risk, in the form of pre-exposure prophylaxis (PrEP). In this study, mathematical HIV models are used to investigate the impact of PrEP as a pre-infection intervention in combination with other interventions, on HIV incidence and prevalence.

We begin the study by recapitulating some key historical events that marked the ascendency of the HIV/AIDS pandemic and PrEP development. Further, we give the motivation of the research study and provide a brief outline.

1.1 Historical background of HIV/AIDS

The origin of HIV/AIDS infection is still complex with various theories developed and some in conflict of each other. Some researches documented that HIV/AIDS started in Haiti [1, 2], while other opinions allegedly claimed that HIV is an experimental man-made and purposely introduced into the American gay-men community and black African populations as a germ warfare experiment in 1970s. For some religious people, AIDS as a disease is a curse from God to punish homosexual individuals and illicit drugs users. However, it is also widely accepted that HIV/AIDS has originated from animal species: the chimpanzees in Kinshasa, the capital city of Republic of Zaire, in 1920 [3]. It is believed that HIV was transferred into the human population by the chimpanzee hunters and consumers who were exposed to animals' infected blood [4]. Evidence of disease crossover has been seen available in the case of avian influenza viruses, bird flu, swine flu and Ebola [5, 6, 7].

Up until 1981, AIDS was classified under rare types of diseases including Pneumocystis carinii pneumonia (lung infection) [8], Kaposi's sarcoma (a kind of cancer) [9], and other unknown deadly diseases that erupted in those years. The first diagnosed patients of Pneumocystis carinii pneumonia (PCP) and Kaposi's sarcoma were mostly among men who had sex with other men (MSM). These patients commonly presented an immune deficiency, exposing them to any opportunistic diseases. The PCP syndrome and Kaposi's sarcoma were often labelled to suggest that this was related to the gay population in America. For instance, in California and New York city, the PCP disease was known as gay-related immune deficiency (GRID) [10], whilst gay-cancer was attributed to Kaposi's sarcoma. In Africa, in rural areas of Uganda, the PCP syndrome is known as 'slim' disease [11], due to the awful weight loss that presented in most ill individuals at their symptomatic stage of the disease. However, unlike the predominance of the syndrome among the gay-men in America, in Uganda the PCP syndrome was reported

among men as well as women. Thus, PCP and Kaposi's sarcoma were no longer classified as being endemic only to gay populations.

In September 1982, in agreement with the international scientific committee, the CDC redefined the GRID syndrome as Acquired Immune Deficiency Syndrome (AIDS) [12]; the first time the term AIDS was officially used. Many AIDS cases were subsequently reported in different countries across South and North America, Africa, Europe, and Australia. AIDS-related healthcare organisations were then set up and extensive studies were undertaken by various group of researchers [13].

In May 1983, health officials in France announced that AIDS could be caused by a virus that they called Lymphadenopathy-Associated Virus (LAV) [14]. A year later, the National Cancer Institute in U.S. working on Kaposi's sarcoma cancer reported that AIDS was caused by a virus that they named HTLV-III (human T-cell lymphotropic virus-type III) [15]. In May 1986, the international scientific committee agreed to call the causative virus of AIDS, HIV (Human Immunodeficiency virus), in place of LAV/HTLV-III [16]. Later, an international group of researchers reported to CDC that HIV is transmitted via (unsafe) sexual contacts, infected blood tools (sharing needles or syringes), infected pregnant mother to child (at birth or through breastfeeding), and during blood transfusion. It was also found that HIV lives off the blood cells ($CD4^+$ T-cells), which are the human body immune guards.

In March 1987, the first antiretroviral (ARV) drug, zidovudine (AZT), was approved by the U.S. Food and Drug Administration (FDA) and became the first life-saving medication for HIV/AIDS treatment [17]. That constituted a great turning point in the fight against HIV infection spread. Later, several distinct types of ARV drugs were developed and recommended to be used in a single dose but more preferably in combination of two or three known as an AIDS 'cocktail' and later as HAART (Highly Active Antiretroviral Therapy). HAART use changed the life expectancy of many individuals living with HIV infection and averted many AIDS-related deaths. However, HIV cases continued to rise steeply. At the United Nations (UN) General Assembly in October 1987, many issues including HIV educational campaigns for global HIV awareness were addressed. As a result, December 1 of each year was declared

to be the World AIDS Day first commemorated, on 1st December 1988 [18]. Three years later, the Visual AIDS Artists Caucus launched the Red Ribbon Project to create a visual symbol to demonstrate compassion for people living with AIDS and their caregivers. The red ribbon became the international symbol of AIDS awareness [19].

Between 1990 and 2000, the HIV epidemic increased and reached a peak. In July 2002, HIV/AIDS was classified as the leading cause of death in Africa. Sub-Saharan Africa was classified (and still is) the worst affected region in the world. In 2013, it was reported that more than 71% of people living with HIV in world resided in Sub-Saharan Africa [20]. In the U.S., HIV was prevalent in large U.S. metropolitan areas (82% in 2014), with Baton Rouge, Miami, and New Orleans topping the list of the areas most heavily burdened [21]. In Asia, China, India and Indonesia account for about three-quarters of the total number of people living with HIV.

In 2015, more than 2.1 million people became newly infected worldwide, adding up to a total of 36.7 million people living with the virus and 1.1 million people died from HIV/AIDS-related illness [24]. According to recent WHO data, approximately 78 (69.5–87.4) million people have become infected with HIV, and 35 (29.6–40.8) million have died from HIV/AIDS, since 1981 [24].

1.2 Advances in HIV/AIDS prevention approaches

There are multi-purpose prevention strategies and technologies currently being developed for effective protection against new HIV infections [22, 23]. In the last 20 years, ARV drugs use has been helpful in mitigating the endemicity of the HIV pandemic. The recent UNAIDS reported that 17 million of people living with HIV are receiving ARV treatment [24]. ART programmes have globally averted an estimated 7.8 million deaths between 2000 and 2014 [25]. ART has also been a great success in prevention of mother to child transmission . HPTN 052 studies demonstrated that consistent ARVs uptake by the HIV-positive partner reduces 96% of the risk of infecting his/her HIV-negative partner [26]. A meta-analysis of 50 publications related

to discordant couples studies found a 91% reduction in per-partner HIV incidence among couples using ART [27]. Moreover, risk behaviour change education has contributed greatly in halting the spread of HIV. Medical male circumcisions have also proven, in many observational studies, to reduce HIV acquisition by approximately 60% [28, 29]. Female and male condoms use have been a powerful weapon in the fight against new infections. Governmental health stakeholders and world health authorities continue to improve the effectiveness of the available male and female condoms. Recently, the South African government proposed a new type of male condom to meet the demands of the population [30, 31]. In Gabon, Donatien Mavoungou with his collaborators presented a drug, namely IMMUNOREX DM28, in the capacity of an HIV vaccine [32]. Studies are currently being conducted to analyse the rare genes that some individuals naturally possess and which make them resistant to HIV infection, with a view to design therapies that confer the same resistance.

More recently, UNAIDS proposed the Fast-Track (the '90-90-90' intervention) treatment targets, where by 2020, 90% of people living with HIV infection worldwide should be diagnosed, 90% of these diagnosed people should have enrolled in ART, and 90% of people receiving ART should have a viral load suppressed [33]. Scientists strongly believe that if the 'triple 90' strategy is fully adopted worldwide and effectively implemented, total and systematic eradication of HIV pandemic will be reached by 2030. While many low-income and middle-income countries are struggling to achieve the 'triple 90' goals, Sweden became the first country to achieve these goals, in September 2016 [34].

1.3 Pre-Exposure Prophylaxis (PrEP)

One of the potential HIV infection prevention measures currently undergoing trials is the use of ARVs in the form of PrEP. PrEP is a preventive approach against sexual HIV transmission. It consists of administering ARVs agents to uninfected individuals at high risk of infection. So far, the biological safety and the effectiveness levels of the PrEP strategy have been explored with two typical ARVs, namely, Tenofovir Disoproxil Fumarate (TDF) or Truvada (a co-formulation of TDF and emtricitabine), available in form of a vaginal gel or rectal microbicide, oral pills,

long-acting vaginal rings, and intramuscular injectables [35, 36]. PrEP trials with both drugs were carried out (and are still ongoing) in different high risk populations of sexually active men and women, including stable serodiscordant couples, sex workers, injecting drug users (IDU), transgenders, and men who have sex with men (MSM), in Africa, Asia, and USA [38, 39, 41]. Results from these trials demonstrated a significant risk reduction in HIV transmission.

The TDF2 studies, launched in Botswana among 1,219 sexually active young adults men and women showed a 63% efficacy of a consistent daily oral Truvada [38]. In Kenya and Uganda, the Partners PrEP studies evaluating both TDF and Truvada in 4,758 heterosexual couples found a 67% HIV transmission risk reduction for a daily oral TDF and 75% for Truvada [39]. In the iPrEx PrEP trial that targeted MSM and transgender women who have sex with men, PrEP effectiveness was rated at 44% for daily Truvada intake [37]. In South Africa, the CAPRISA 004 trial on 889 heterosexual women, reported that regular use of TDF in the form of a vaginal microbicide gel (1%) lowered HIV incidence by 39% overall and 54% for high adherence, that is, at least 80% of prescribed doses [40]. Results from a Thai study in IDU populations indicated that a strict daily oral TDF regimen shrunk HIV transmission odds by 49% [41]. Despite the disparities noticed in the results from these trials, effective protection is accredited to Truvada use. Thus, in July 2012, the U.S. FDA recommended Truvada for PrEP use for optimal protection benefits. Several PrEP studies targeting people at risk of HIV infection transmission exposure in different parts of the world are still underway (see Figure 1.1).

1.4 Upcoming PrEP trials

Numerous ongoing improvement of PrEP interventions including testing new dosing regimens and new drugs are envisioned. In May 2014, the U.S. CDC released new clinical practice guidelines for PrEP. These guidelines addressed the challenges regarding PrEP use in stable serodiscordant couples wishing to conceive naturally [43]. New ARVs agents including dapivirine, rilpivirine, maraviroc, and new integrase inhibitors are under investigation for PrEP use [44]. The ongoing HPTN-069/ACTG-530 trial is assessing the safety of maraviroc as PrEP com-

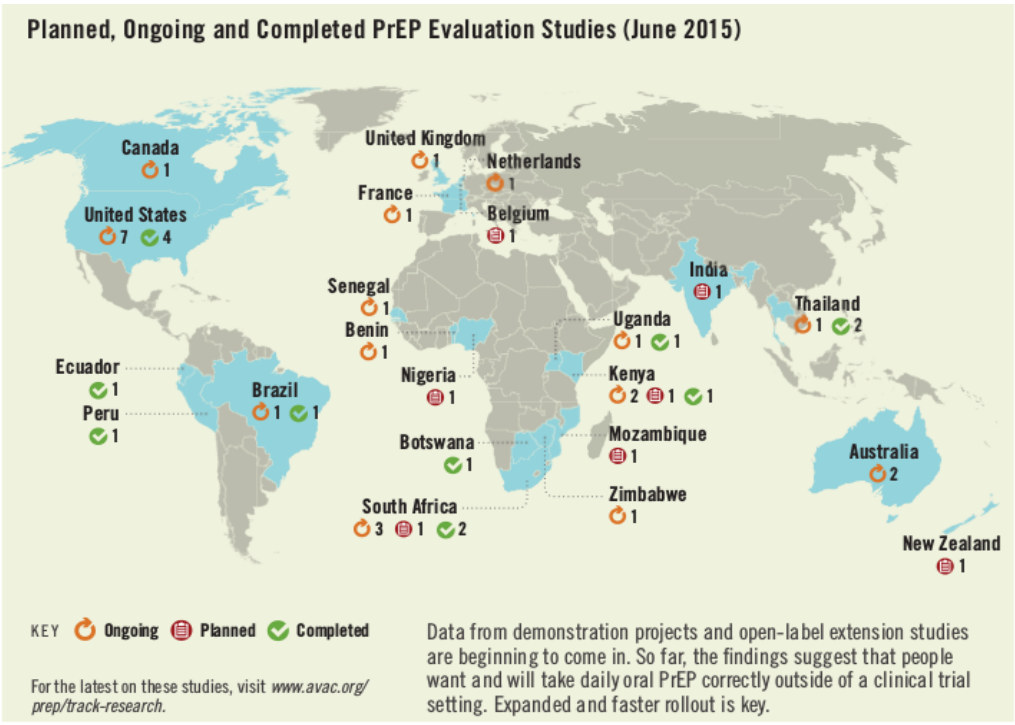

Figure 1.1: Planned, Ongoing, and Completed PrEP Evaluation Studies (June 2015) [42].

pared to Truvada protection among MSM, heterosexual men and women, and transgender men in thirteen cities in USA [45]. The RING and ASPIRE–MTN020 trials in Malawi are evaluating the Dapivirine intravaginal ring [44]. Phase 1 trials are being conducted of long-acting injectables which would transform PrEP from daily pill-taking to 3 months injection [46]. Tremendous new drug formulations and prevention strategies are under development, including gels, films, long-acting vaginal rings and injectables, and technologies [47, 35]. The PROUD trial [48] in the U.K and the IPERGAY trial [49] in France are also some of the ongoing PrEP intermittent dosing studies. The Follow-on African Consortium for Tenofovir Studies (FACTS) 001 trials is enrolling women aged between 18 and 30 across nine sites in South Africa for another trial of the TDF 1% vaginal gel. FACTS is assessing the protective benefit of TDF 1% vaginal gel applied pre- and post-intercourse for HIV and HSV-2 prevention. FACTS 002 is in the planning phase for a similar trial among adolescent women aged between 16 and 17 [50].

1.5 Abandoned PrEP trials

Despite the aforementioned great advances in PrEP interventions and HIV infection prevention measures, some PrEP trials presented limitations and shortcomings resulting early termination. The FEM-PrEP trial assessing the prevention benefit of daily oral Truvada in Kenyan was prematurely interrupted due to a lack of protection [51]. The VOICE trail (MTN-003) which investigated daily TDF vaginal gel among 5,029 heterosexual African women was discontinued due to its futility [52]. Early PrEP trials have also faced dramatic objections and emerging protests from activist groups and affiliated non-governmental organisations especially in 2004–2005. In July 2004, PrEP trial funded by the United States National Institutes of Health and the Bill and Melinda Gates Foundation in Cambodia was halted due to the increased protests of activist groups [53, 54]. In 2005, a PrEP trial in Cameroon, led by Family Health International (FHI), was prematurely interrupted by the Minister of Public Health [54]. Earlier that year, FHI announced the discontinuation of the 'fragile' TDF PrEP trial in Nigeria, due to the lack of compliance of the required operational and laboratory procedures at the level necessary for purpose of the study [54]. In a documentary broadcasted on French media and subsequently on other media, activists speculated that the FHI investigators intentionally exposed participants to high risk of infection by providing only five counsellors for 400 participants [55]. In May 2005, a meeting among activists representatives, advocacy and research groups leaders conducted by the Bill and Melinda Gates Foundation sought resolution by providing deep and comprehensive information and knowledge about PrEP use benefits.

1.6 Motivation

New approaches to HIV/AIDS prevention and HIV cure are urgently needed to stop the cumulative number of new HIV infections that occur every year across the world. New strategies as well as prophylactic agents were recently released and tested through different studies to assess their capacity to suppress the viral load of already-infected individuals or to prevent the uninfected at high risk of infection. Of these strategies, the PrEP strategy that refers to

the use of ARV drugs (Tenofovir or Truvada) before risky sexual exposure is the current HIV prevention intervention that holds most promise. PrEP strategy is proven in various clinical trials to reduce the risk of sexual HIV transmission. However, the results obtained from these studies are complex with diverse findings thereby exposing the need to pursue more investigations that might give broader insights into the protection benefits of PrEP and provide useful information for effective implementation of PrEP strategy outside the trial world. While no conclusive reasons are yet given for the striking differences reported from these trials, considerations focus on adherence levels of PrEP users to the drug and the efficacy of drug. Other concerns point to the acceptability of the drugs outside the shaped trial zone. Drug resistance that might jeopardize the therapeutic benefits of PrEP use is also a cause for worry.

PrEP implementation at a population level is gaining much more attention and more research is needed to better define and determine the required level of adherence to PrEP use, the preferable dosing of the drugs, affordability of PrEP drug, medical risk of PrEP drugs intake in long-term use, the impact of drug resistance on PrEP effectiveness, to whom PrEP drug should be prescribed and when and by whom, the benefit in combining PrEP use with other effective pre-existing interventions, etc. This project thus seeks to investigate and give more insights into the impact of these factors in PrEP implementation and PrEP in combination with other strategies via mathematical modelling. Mathematical models are developed and analysed incorporating some of the aforementioned factors to give insights into PrEP impact on HIV incidence and prevalence. PrEP associated with other prevention measures such as early ART will be considered, and PrEP in combination with risk behaviour change education will be examined. We expect that the knowledge gained from this study will partially contribute to better decision making by health stakeholders and the establishment of HIV care policies that might help to effectively implement PrEP strategies in communities and help in bringing the HIV pandemic under control.

1.7 Objectives of the study

The aim of this research project is to formulate mathematical models that can be used to investigate the impact of PrEP intervention and PrEP interventions used with control strategies on HIV infection dynamics at a population level.
The primary objectives are

(i) To explore different PrEP intervention scenarios considering distinct levels of adherence and efficacy in PrEP use at a population level.

(ii) To investigate the impact of combining PrEP intervention and early antiretroviral drug therapy in the fight against new HIV infections.

(iii) To highlight the relative contribution of PrEP drug resistance in HIV spread and its impact on the therapeutic benefits of PrEP use.

(iv) To analyse the impact of post HIV educational support service and the effect of time dependent control (policies) in PrEP intervention through optimal control.

1.8 Outline of the study

This thesis is presented in integrated-articles form that constitute chapter 2, chapter 3, and chapter 4. Of the first three articles, two are under review while one is accepted with minor revision.

- In Chapter 2, we formulate a PrEP model to analyse four distinct PrEP interventions considering PrEP adherence and PrEP efficacy as key control factors. Rigorous mathematical analysis and numerical simulations are carried out and novel model observations emanating from the model analysis are presented.

- In Chapter 3, factors such as PrEP drug resistance and early antiretroviral use are incorporated in the PrEP model for analysis. Mathematical analyses and numerical simulations are given.

- In Chapter 4, optimal control theory is applied to a PrEP model while HIV infection educational support service is incorporated and other important social factors as the discontinuation of PrEP intake are factored in.
- In Chapter 5, we give a comprehensive conclusion of our findings and recommendations.

1.9 Publications

This thesis is built around the following papers

Chapter 2

- Komi Afassinou, Faraimunashe Chirove and Keshlan S. Govinder (2016), Comparing strategies of PrEP use and PrEP awareness on HIV infection progression, *BioSystems*, (*Under review*).

Chapter 3

- Komi Afassinou, Faraimunashe Chirove and Keshlan S. Govinder (2016), Pre-exposure prophylaxis and antiretroviral treatment interventions with drug resistance, *Mathematical Biosciences*, (*Accepted with minor revision and under revision*).

Chapter 4

- Komi Afassinou, Faraimunashe Chirove and Keshlan S. Govinder (2016), Optimizing PrEP and post-HIV infection control strategies, Journal of Nonlinear Analysis: Real World Applications (*Under review*).

Chapter 2

Comparing strategies of PrEP use and PrEP awareness on HIV infection progression

Comparing strategies of PrEP use and PrEP awareness on HIV infection progression

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Abstract

We present a compartmental HIV/AIDS model incorporating pre-exposure prophylaxis (PrEP) use and PrEP efficacy and investigate different strategies capturing the level of PrEP use and PrEP efficacy. Mathematical analysis is carried out and important mathematical features of the model such as the epidemic threshold parameter, the equilibrium points and stability conditions thereof are presented. The threshold parameter of the model is rigorously analysed and sensitivity analysis is conducted to get more insights into the HIV infection transmission dynamics in presence of PrEP. Our results reveal that the model on PrEP use and efficacy is a parameter connected model where the connecting parameter is dependent on PrEP awareness. The strategy with high PrEP use and high PrEP efficacy level is shown to be the best but may not continuously keep the HIV burden under check.

Keywords: PrEP, HIV, PrEP awareness, PrEP efficacy.

1. Introduction

HIV infection prevention by means of abstinence or mutual monogamy practice with an HIV-negative partner remains the first line of defence against the virus. Although the method is more effective, it is not fully practised by many individuals in different communities. Antiretroviral use and correct use of condoms before any sexual activity were demonstrated to be highly potent and fundamental strategies against HIV infection. Pre-exposure HIV prophylaxis (PrEP) in general is a healthy preventative measure for the control of an infection. This includes the use of male/female condoms, male circumcision, prophylactic vaccines, vaginal and rectal microbicide and systemic administration of HIV antiretrovirals [1].

PrEP for HIV infection consists of either of microbicide or antiretroviral drugs (ARVs). We shall focus on the latter when taken by uninfected individuals who are at risk of getting infected. The benefits of PrEP involves direct protection of PrEP users and

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indirect protection of non-PrEP users leading to reduce numbers of HIV infections due to decreased transmission [2, 3, 4]. The concept of using ARVs as a preventive method was successful in prevention of mother-to-child transmission of HIV. It was shown in animal studies that the proper timing of PrEP use can effectively prevent HIV infection whilst the inappropriate timing may lead to partial prevention of HIV infection [4]. Recent studies showed that HIV PrEP using ARVs such as Tenofovir/TDF (Tenofovir Disoproxil fumarate) and Truvada/TDF-FTC (TDF co-formulated with emtricitabine) substantially reduced the risk of acquiring HIV infection [5]. A large number of clinical trials have been undertaken (and still undergo) in various heavy HIV affected settings across the world. Results obtained from these studies have confirmed and spotlight the potential impact of PrEP interventions on HIV infection incidence. In the iPrEx study [6], 2,499 HIV-negative men who have sex with men (MSM) were randomly enrolled out to receive daily oral pill of the fixed-dose combination tablet of emtricitabine and tenofovir disoproxil fumarate (that is Truvada) or placebo associated with comprehensive prevention services provided. The results obtained showed a relative reduction in risk infection of 44%. Nonetheless, it was demonstrated throughout the studies that in case of optimal adherence, the HIV incidence could be reduced by 92% [6]. The TDF2 trial conducted by the Centers of Disease Control investigated the protective efficacy level of once-daily oral pill of Truvada in 1,219 heterosexual men and women in Botswana [7] whilst the Partners PrEP trial evaluated the effectiveness of the Tenovofir and Truvada in 4,758 HIV serodiscordant couples in Kenya and Uganda [8]. In Both PrEP regimen, results showed an effective risk infection reduction by 62% for the Tenofovir gel whereas Truvada was found 73% effective. The CAPRISA004 study on 899 South African women showed 39% of risk reduction on HIV acquisition when one considers TDF gel in form of vaginal gel [9]. In their study the tenofovir gel was recommended to be applied in the women genital part for two times in a 24 hours period; one dose within 12 hours before sexual acts and another, as soon as possible, within the next 12 hours after sex [9]. Some argue that one of the great advantage of Tenofovir gel when used by women is that, women at risk can use it without their partner's knowledge, avoiding any systematic objections from the partner. PrEP interventions in HIV infection prevention potentially had a profound impact and has gained much attention, in the last decade, around the word [10, 11, 12]. Various clinical trials still undergo phases testing across the world to refine the existing PrEP use policies and suggest better comprehension information regarding PrEP use; these trials include MTN VOICE, CAPRISA, TDF2, Partners FEM-PrEP. Thus, PrEP is likely to be added to the list of the pillars of HIV comprehensive prevention strategies. Of note, PrEP efficacy and PrEP use awareness are some of the important factors which affect PrEP intervention. The two factors can contribute to low prevention or high prevention depending on the strategy used [13].

Mathematical PrEP models analyses in the last years have also supported the potential role that played PrEP use in HIV infection reduction in communities. Ashrafur *et al.* in [13] investigated the impact of Tenofovir gel as a PrEP on HIV infection. Their results showed that the effectiveness of the gel largely depends on the level of adherence to the gel and the proportion of women under gel coverage. The authors in

[14] studied the interactions between PrEP interventions and treatment programs in resource-constrained countries. Their results spotlighted the potential benefits of PrEP intervention when a high "quality" of PrEP is taken into account. Visser *et al.* [4] used mathematical models to fit data collected from some countries which rolled out PrEP use in high risk population. Their model captured a certain number of factors affecting PrEP use such gender, level of risk, state of infection and PrEP intake. To the best of our knowledge, PrEP awareness and PrEP efficacy have not yet been considered in mathematical PrEP models analyses. We strongly believe that these two factors need to be taken into account for an effective PrEP implementation.

In this study, we shall investigate the impact of PrEP strategies involving the level of PrEP use awareness and the efficacy of PrEP in a community. We shall do this by testing the benefits of administering the following strategies: (i) low PrEP use and low PrEP efficacy, (ii) low PrEP use and high PrEP efficacy, (iii) high PrEP use and low PrEP efficacy and (iv) high PrEP use and high PrEP efficacy. We shall compare the effects of these strategies to a scenario with no PrEP use at all.
The model formulation shall be presented in section 2, the model essential proprieties in section 3, model analysis in section 4, numerical simulations in section 5 and discussion of results in section 6.

2. Model Formulation

We partition the human population into five classes, namely: susceptible non-PrEP users S, susceptible PrEP users S_p, infected non-PrEP users I, infected PrEP users I_p, and AIDS individuals A. We assume that all at risk individuals are recruited into the non-PrEP susceptible class when they are sexually active at constant rate π. Whilst in this class, individuals are exposed to PrEP use awareness and decide whether or not to use PrEP as a priority preventative measure. A proportion γ, $0 \leq \gamma \leq 1$, responds positively to PrEP use whilst the remaining proportion, $(1-\gamma)$, does not. By responding positively to PrEP use, we mean acceptance and consistence intake of PrEP drug provided. Individuals who accept PrEP will immediately start using it and move to the class of susceptible PrEP users and those who do not respond to PrEP use will remain in the non-PrEP susceptible class. Reasons for not responding to PrEP use span from cultural and religious beliefs, to inadequate PrEP awareness campaigns amongst others. The non-PrEP susceptible individuals are removed from this class through either natural death or through HIV infection due to unsafe sexual practices. PrEP users are assumed to continue using PrEP until they leave the class. The susceptible PrEP users move out of their class through either natural death or HIV infection due to PrEP protection failure. We use PrEP efficacy $\sigma, 0 \leq \sigma \leq 1$, as a measure for PrEP protection. Thus $(1-\sigma)S_p$ individuals are exposed to successful HIV infection due to PrEP protection failure.

Non-PrEP users who become infected with HIV move to a new class of infected non-PrEP users I through a force of infection $\lambda(I, I_p, A)$. They leave the class through either natural death or progression to AIDS at a rate ρ_1. Individuals who become infected

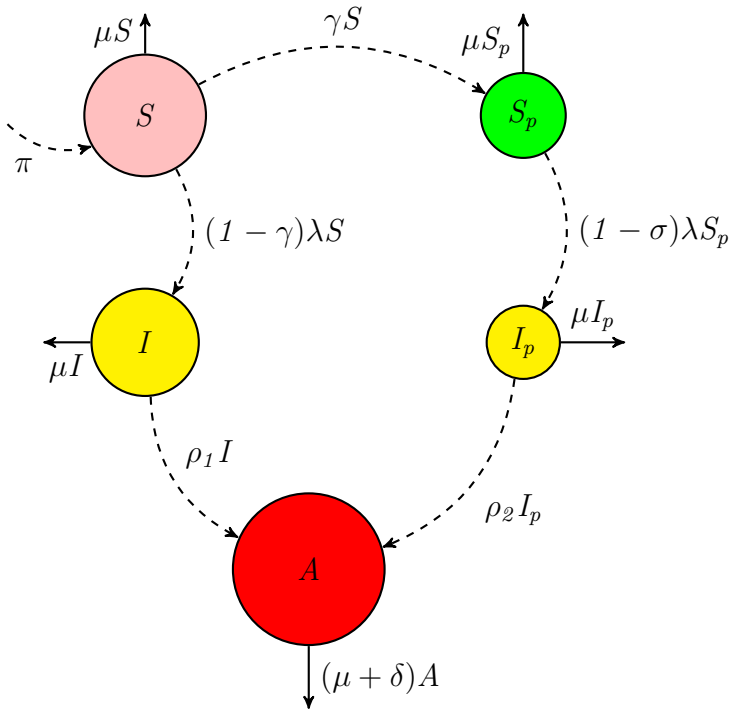

Figure 1: Flow diagram for the pre-exposure HIV prophylaxis model.

due to PrEP protection failure move to the class of infected PrEP users and leave the class through natural death or progression to the AIDS class A at a rate ρ_2. AIDS individuals die naturally or die due to AIDS at a rate δ. We assume that the natural death rate μ is the same for all the five classes. We define the total human population as the sum of all individuals in the five classes as

$$N(t) = S(t) + S_p(t) + I(t) + I_p(t) + A(t). \tag{1}$$

We represent our compartmentalized model through the flow diagram in Figure 1. The change in the flow of individuals in the five classes is governed by the system of nonlinear ordinary differential equations given by

$$\begin{aligned}
\dot{S} &= \pi - \gamma S - (1-\gamma)\lambda S - \mu S, && (2)\\
\dot{S}_p &= \gamma S - (1-\sigma)\lambda S_p - \mu S_p, && (3)\\
\dot{I} &= (1-\gamma)\lambda S - (\rho_1 + \mu) I, && (4)\\
\dot{I}_p &= (1-\sigma)\lambda S_p - (\rho_2 + \mu) I_p, && (5)\\
\dot{A} &= \rho_1 I + \rho_2 I_p - (\mu + \delta) A, && (6)
\end{aligned}$$

where the upper dot represents the derivative of the component with respect to time t. We consider the force of infection to be

$$\lambda(I, I_p, A) = \frac{c(I + \eta_1 I_p + \eta_2 A)}{N}, \tag{7}$$

where $\eta_1 < 1$ denotes the measure of the impact of the infected PrEP users towards HIV infection compared to the contribution from non-PrEP infected individuals and AIDS individuals. A similar explanation is valid for $\eta_2 > 1$ with regards to the contribution of AIDS individuals. The probability of a successful HIV infection transmission resulting from unsafe sexual contact between an infected individual and a susceptible individual is denoted by c.

3. Positivity and boundedness of the solutions of the model

The time evolution of the population of each class defined is revealed by the solutions of system (2)-(6). Like any dynamical system, it is important to ensure the well-posedness of the system so that the solutions reflect the natural phenomenon or the process described. Thus, in our case for the solutions of the system (2)-(6) to be biologically meaningful, we should guarantee the positivity and boundedness of these solutions for all the time $t \geq 0$.
Considering the first equation (2), we define its integrating factor as follows

$$\psi(t) = \exp\left\{\int_0^t (\mu + \gamma + (1-\gamma)\lambda(\tau))d\tau\right\},$$

so that

$$\frac{d}{dt}\left(S(t)\psi(t)\right) = S(t)\frac{d\psi(t)}{dt} + \frac{dS(t)}{dt}\psi(t) = \pi \exp\left\{\int_0^t (\mu + \gamma + (1-\gamma)\lambda(\tau))d\tau\right\}.$$

This gives

$$\begin{aligned} S(t) &= \exp\left\{-\int_0^t (\mu + \gamma + (1-\gamma)\lambda(\tau))d\tau\right\}\left(\int_0^t \pi \exp\left\{\int_0^s (\mu + \gamma + (1-\gamma)\lambda(r))dr\right\}ds\right) \\ &+ S(0)\exp\left\{-\int_0^t (\mu + \gamma + (1-\gamma)\lambda(\tau))d\tau\right\}, \end{aligned}$$

where $S(0)$ is a given initial value of $S(t)$. It follows that $S(t)$ is non-negative for all the time if $S(0)$ is non-negative. This indicates that the population variable $S(t)$ will remain non-negative for $t \geq 0$.
Similarly, the other population variables can be proven non-negative using the corresponding equation of the system. This shows that the solutions of the system (2)-(6) with non-negative initial conditions will remain non-negative for all time $t \geq 0$. We state this result as follows:

Lemma 1. *If the given initial conditions $S(0)$, $S_p(0)$, $I(0)$, $I_p(0)$, and $A(0)$ of the system (2)-(6) are non-negative, then so are the resulting solutions $S(t)$, $S_p(t)$, $I(t)$, $I_p(t)$, and $A(t)$ for all the time $t \geq 0$.*

Moreover, adding all the equations (2)-(6) yields

$$\begin{aligned} \dot{N} &= \pi - \mu N - \delta A \\ &\leq \pi - \mu N. \end{aligned} \tag{8}$$

Solving the inequality (8) gives

$$N(t) \leq \frac{\pi}{\mu} + \left(N(0) - \frac{\pi}{\mu}\right) e^{-\mu t}, \tag{9}$$

where $N(0)$ is the initial value of $N(t)$. It can be seen that if $N(0) \leq \frac{\pi}{\mu}$ then $N(t) \leq \frac{\pi}{\mu}$ for $t \to \infty$. Hence, $\frac{\pi}{\mu}$ an is upper bound of $N(t)$ and subsequently, for all the solutions of the system. On another hand, if $N(0) > \frac{\pi}{\mu}$ then $N(t)$ will decrease to $\frac{\pi}{\mu}$ as $t \to \infty$, that is, all the solutions of the system converge to $\frac{\pi}{\mu}$ as time goes. In both situation, $\frac{\pi}{\mu}$ is the upper bound of all the solutions. We therefore define the region

$$\mathcal{B}_f = \left\{(S, S_p, I, I_p, A) \in \mathbb{R}^5_+ | S \geq 0,\, S_p \geq 0,\, I \geq 0,\, I_p \geq 0,\, A \geq 0,\, N \leq \frac{\pi}{\mu}\right\},$$

as the biological feasible region of the solutions of our model.
From what precedes, it is clear that all solutions of the system starting in the region $\mathcal{B}_f$ will remain inside for all the time whereas all solutions starting in the neighbourhood of $\mathcal{B}_f$ will enter or approach it asymptotically. The region $\mathcal{B}_f$ is thus said to be positively invariant and biologically tractable, under the flow induced by the system. We shall therefore confine our model analysis to the region $\mathcal{B}_f$.

4. Model analysis

We carry out the model analysis exploring the stability conditions of the equilibrium points of the system (2)-(6). We shall use the epidemic threshold parameter $\mathcal{R}_0$, that is, the basic reproduction ratio of our model to establish the stability analysis. Further, sensitivity analysis of $\mathcal{R}_0$ shall be conducted to help identifying policies or intervention strategies that would be used to reduce HIV infection prevalence when a particular parameter value is subjected to a perturbation.

4.1. The basic reproduction ratio $\mathcal{R}_0$

The basic reproduction ratio of our model is an important threshold that is used to predict conditions under which HIV infection is most likely to progress or regress in the presence of PrEP use awareness and PrEP efficacy. The basic reproduction ratio for the system of equations (2)-(6) is calculated using the next generation matrix method in [15]. Conforming to the same notations as in [15], the matrices $\mathbf{F}$ and $\mathbf{V}$ for the new infection terms and the remaining transfer terms are respectively given by

$$\mathbf{F} = \begin{pmatrix} \frac{c\mu(1-\gamma)}{\mu+\gamma} & \frac{c\mu(1-\gamma)\eta_1}{\mu+\gamma} & \frac{c\mu(1-\gamma)\eta_2}{\mu+\gamma} \\ \frac{c\mu(1-\sigma)}{\mu+\gamma} & \frac{c\mu(1-\sigma)\eta_1}{\mu+\gamma} & \frac{c\mu(1-\sigma)\eta_2}{\mu+\gamma} \\ 0 & 0 & 0 \end{pmatrix} \quad \text{and} \quad \mathbf{V} = \begin{pmatrix} \rho_1+\mu & 0 & 0 \\ 0 & \rho_2+\mu & 0 \\ -\rho_1 & -\rho_2 & \mu+\delta \end{pmatrix}.$$

The basic reproduction ratio of the system defined as the spectral radius of the next generation matrix ($\mathbf{FV^{-1}}$) is given by

$$\mathcal{R}_0 = \frac{c\mu(1-\gamma)(\mu+\delta+\rho_1\eta_2)}{(\gamma+\mu)(\mu+\rho_1)(\mu+\delta)} + \frac{c\gamma(1-\sigma)(\eta_1(\mu+\delta)+\rho_2\eta_2)}{(\gamma+\mu)(\mu+\rho_2)(\mu+\delta)}. \tag{10}$$

Epidemiologically, the basic reproduction ratio $\mathcal{R}_0$ represents the expected number of the secondary infections that result from introducing a single infected individual into a pure susceptible population where PrEP program is implemented.
To get better understanding of the basic reproduction ratio $\mathcal{R}_0$, we give biological significance of each of its components. In the first component, the terms $\frac{1}{(\rho_1+\mu)}$ and $\frac{1}{\delta+\mu}$ indicates the average period of time that an infected individual spends in $I(t)$ class and $A(t)$ class, respectively. The terms $\frac{c}{\rho_1+\mu}$ and $\frac{\rho_1}{(\rho_1+\mu)}.\frac{c\eta_2}{(\delta+\mu)}$ are the probabilities that a typical susceptible individual being infected by an individual in $I(t)$ class and $A(t)$ class, respectively. Thus, in the first component the term, say, $\mathcal{R}_1 = (1-\gamma)\left(\frac{c}{\rho_1+\mu} + \frac{\rho_1}{(\rho_1+\mu)}.\frac{c\eta_2}{(\delta+\mu)}\right)$ is the proportion of new HIV infections caused by an infected non-PrEP user or AIDS individual, whilst the factor $\kappa = \frac{\mu}{(\gamma+\mu)}$ measures the effectiveness of the PrEP awareness. Clearly, when γ increases, to mean when more susceptible individuals are enrolling in PrEP use, the factor κ is reduced, therefore $\mathcal{R}_1$ is reduced. The infection rate $\mathcal{R}_1$ is therefore reduced when γ increases. In other words, this indicates that the more the susceptible individuals are on PrEP use, the more the infection rate $\mathcal{R}_1$ is reduced.
A similar relevant significance can also be given to each term in second component where the term, say, $\mathcal{R}_2 = (1-\sigma)\left(\frac{c\eta_1}{\rho_2+\mu} + \frac{\rho_2}{(\rho_2+\mu)}.\frac{c\eta_2}{(\delta+\mu)}\right)$ models the proportion of new HIV infections caused by an infected PrEP user and AIDS individual.
Upon giving these analyses, we re-write the basic reproduction ratio $\mathcal{R}_0$ in terms of $\mathcal{R}_1$, $\mathcal{R}_2$, and κ to obtain

$$\mathcal{R}_0 = \kappa\mathcal{R}_1 + (1-\kappa)\,\mathcal{R}_2, \tag{11}$$

where

- $\mathcal{R}_1$ models the proportion of new infections caused by a non-PrEP infected individual and an AIDS individual, whilst
- $\mathcal{R}_2$ models the proportion of new infection caused by a PrEP infected individual and AIDS individuals, and
- κ measures the effectiveness of the PrEP awareness.

We shall define $\mathcal{R}_{slow} = \min\{\kappa\mathcal{R}_1, (1-\kappa)\mathcal{R}_2\}$ as the slow reproduction ratio and $\mathcal{R}_{fast} = \max\{\kappa\mathcal{R}_1, (1-\kappa)\mathcal{R}_2\}$ as the fast reproduction ratio. Thus, we call the parameter κ $(0 < \kappa \leq 1)$, the slow-fast parameter. The PrEP model (2)-(6) is said to be a parameter connected model.

Definition 1. *An epidemiological model*

$$(\mathcal{S}) : \dot{x} = f(x), \quad x \in \mathbb{R}^n_+$$

is said to be a ***parameter connected model****, if there exists a partition of that model into two sub-models* $(\mathcal{S}_1)$ *and* $(\mathcal{S}_2)$ *such that the basic reproduction ratio of the model*

($\mathcal{S}$) connected by a parameter κ, is a linear combination of basic reproduction ratios, $\mathcal{R}_1$ and $\mathcal{R}_2$, of the sub-models ($\mathcal{S}_1$) and ($\mathcal{S}_2$) satisfying

$$\mathcal{R}_0 = \kappa\mathcal{R}_1 + (1-\kappa)\mathcal{R}_2. \tag{12}$$

Theorem 1. *The PrEP model (2)-(6) is parameter connected model.*

Proof. A close observation indicates that in a scenario where PrEP is 100% efficacious, i.e. $\sigma = 1$, the number of infected individuals due to PrEP protection failure is zero ($I_p = 0$). As a result, the HIV infection dynamics is restrained to the dynamics and interactions between the non-PrEP infected, AIDS individuals, and the non-PrEP susceptible individuals. The system (2)-(6) is reduced to system

$$(\mathcal{S}_1): \quad \begin{cases} \dot{S} &= \pi - (1-\gamma)\dfrac{c(I+\eta_2 A)}{N_1}S - (\mu+\gamma)S, \\ \dot{I} &= (1-\gamma)\dfrac{c(I+\eta_2 A)}{N_1}S - (\rho_1+\mu)I, \\ \dot{A} &= \rho_1 I - (\mu+\delta)A. \end{cases}$$

On the other hand, in a scenario where PrEP use awareness is 100% effective, i.e $\gamma = 1$, the system (2)-(6) is reduced

$$(\mathcal{S}_2): \quad \begin{cases} \dot{S}_p &= \pi - (1-\sigma)\dfrac{c(\eta_1 I_p + \eta_2 A)}{N_2}S_p - \mu S_p, \\ \dot{I}_p &= (1-\sigma)\dfrac{c(\eta_1 I_p + \eta_2 A)}{N_2}S_p - (\rho_2+\mu)I_p, \\ \dot{A} &= \rho_2 I_p - (\mu+\delta)A. \end{cases}$$

In both sub-models, $N_1 = S + I + A$ and $N_2 = S_p + I_p + A$. As early mentioned, the sub-model ($\mathcal{S}_1$) describes interactions and progression dynamics of non-PrEP users while the sub-model ($\mathcal{S}_2$) describes the interactions and progression of PrEP users. It is easy to show that the biological feasible region of both sub-models are

$$\Omega_1 = \left\{ (S, I, A) \in \mathbb{R}^3_+ | S + I + A \leq \frac{\pi}{\gamma + \mu} \right\},$$

and

$$\Omega_2 = \left\{ (S_p, I_p, A) \in \mathbb{R}^3_+ | S_p + I_p + A \leq \frac{\pi\gamma}{\mu(\gamma + \mu)} \right\}.$$

respectively; which are positively invariant and attractive. The reproduction ratios for the sub-models ($\mathcal{S}_1$) and ($\mathcal{S}_2$) are given by

$$\mathcal{R}_1 = \frac{c(1-\gamma)(\mu+\delta+\rho_1\eta_2)}{(\mu+\rho_1)(\mu+\delta)}, \quad \mathcal{R}_2 = \frac{c(1-\sigma)(\eta_1(\mu+\delta)+\rho_2\eta_2)}{(\mu+\rho_2)(\mu+\delta)},$$

respectively. Clearly, the basic reproduction ratio $\mathcal{R}_0$ is a linear combination of the reproduction ratios of sub-models ($\mathcal{S}_1$) and ($\mathcal{S}_2$) generated from the partition of PrEP model. The reproduction ratios $\mathcal{R}_1$ and $\mathcal{R}_2$ are connected by a parameter κ. This completes the proof.

Table 1: PrEP strategies and characterization of reproductions ratios

Case	Strategy	Reproduction ratios		
(a)	Low PrEP use and Low PrEP efficacy	$\mathcal{R}_1 > 1$	$\mathcal{R}_2 > 1$	$\mathcal{R}_0 > 1$
(b)	High PrEP use and Low PrEP efficacy	$\mathcal{R}_1 < 1$	$\mathcal{R}_2 > 1$	$\mathcal{R}_0 > 1$
(c)	Low PrEP use and High PrEP efficacy	$\mathcal{R}_1 > 1$	$\mathcal{R}_2 < 1$	$\mathcal{R}_0 > 1$
(d)	High PrEP use and High PrEP efficacy	$\mathcal{R}_1 < 1$	$\mathcal{R}_2 < 1$	$\mathcal{R}_0 < 1$

Remark 1. The analysis of the parameter connected model for an epidemiological disease is important in the sense that it reveals that the control of infection in a community may need a balance in more than one intervention strategies. Thus in our case, the control will be done by simultaneously monitoring both fast reproduction ratio and the slow reproduction ratio to levels where the epidemic can be managed effectively. Moreover, the parameter connected model allows us to determine the group of individuals in a community who are more susceptible to infection and use the information to channel intervention strategies equitably. A scenario revealing $\mathcal{R}_1 > 1 > \mathcal{R}_2$, for instance, indicates that the PrEP use awareness is at low level while the PrEP efficacy level is at high level. In that particular situation, efforts need to be done to bring the reproduction ratio associated to the fast reproduction ratio (i.e $\mathcal{R}_1$ in this case) under unity or to the convenient level by enhancing the PrEP awareness scopes. In a reverse scenario, efforts will be done to improve the PrEP efficacy level. In Table 1, we present some hypothetical scenarios corresponding to different possible values of the reproduction ratios.

4.2. Analysis of $\mathcal{R}_0$

The basic reproduction ratio of our model captures most of the parameters related to the social factors captured in our model. Thus, a small variation of the magnitude of the basic reproduction ratio is simply a result of a small perturbation of conditions that connect the infection dynamics to one or more of its these parameters. Thus, performing the sensitivity analysis of $\mathcal{R}_0$ with respect to its dependent parameters seems to be crucial for a deep understanding of the HIV infection dynamics in the presence of PrEP intervention. Meanwhile, we shall investigate the impact of the PrEP control parameters, γ and σ, on the basic reproduction ratio.

4.2.1. Impact of γ and σ on $\mathcal{R}_0$

We investigate the effects of PrEP awareness and PrEP efficacy on $\mathcal{R}_0$ by computing the partial derivative of $\mathcal{R}_0$ with respect to γ and σ as follows:

$$\begin{aligned}\frac{\partial \mathcal{R}_0}{\partial \gamma} &= \frac{\kappa^2}{\mu}(\mathcal{R}_2 - \mathcal{R}_1) - \frac{\mu}{1-\gamma}\mathcal{R}_1,\\ \frac{\partial \mathcal{R}_0}{\partial \sigma} &= -\frac{1}{1-\sigma}\mathcal{R}_2.\end{aligned}$$

We note that:

$$\begin{aligned}
\frac{\partial \mathcal{R}_0}{\partial \gamma} &< 0 \text{ for } \mathcal{R}_2 \leq \mathcal{R}_1,\ \gamma \neq 1, && (13)\\
\frac{\partial \mathcal{R}_0}{\partial \gamma} &= 0 \text{ for } \mathcal{R}_2 = \left(1 + \frac{\mu^2}{(1-\gamma)\kappa^2}\right)\mathcal{R}_1,\ \gamma \neq 1, && (14)\\
\frac{\partial \mathcal{R}_0}{\partial \gamma} &> 0 \text{ for } \mathcal{R}_2 > \left(1 + \frac{\mu^2}{(1-\gamma)\kappa^2}\right)\mathcal{R}_1, && (15)\\
\frac{\partial \mathcal{R}_0}{\partial \sigma} &< 0,\ \sigma \neq 1. && (16)
\end{aligned}$$

We also note that

$$\begin{aligned}
\lim_{(\sigma,\gamma)\to(\sigma,1)} \mathcal{R}_0 &= \frac{1}{\mu+1}\mathcal{R}_2, && (17)\\
\lim_{(\sigma,\gamma)\to(1,\gamma)} \mathcal{R}_0 &= \kappa\mathcal{R}_1, && (18)\\
\lim_{(\sigma\gamma)\to(1,1)} \mathcal{R}_0 &= 0. && (19)
\end{aligned}$$

Remark 2. From equation (13), we observe that an increase in PrEP awareness can lead to a reduction of the basic reproduction ratio as long as the infection rate due to infected PrEP users is less than that of infected non-PrEP users. This strategy may require the PrEP efficacy to be maintained high in light of equation (17). This is evident in conditions (17) and (18) where increasing either PrEP awareness only or PrEP efficacy only will reduce and not eradicate the contribution of infected non-PrEP users and/or infected PrEP users towards the progression of HIV infection. Results (13) and (16) also suggest that both PrEP awareness and PrEP efficacy need not be 100% to achieve significant reduction of the basic reproduction ratio. Condition (19) reveals the same but suggests that to significantly reduce the basic reproduction ratio, high levels of PrEP awareness and PrEP efficacy need be employed. Conditions (14) and (15) give a potential warning in the use of PrEP awareness that raising awareness on prophylaxis alone as a strategy may not always work. Efforts should be made to consider the efficacy of PrEP as well.

4.2.2. Sensitivity analysis of $\mathcal{R}_0$

The sensitivity analysis assesses the amount and the type of change inherent in $\mathcal{R}_0$ when a typical dependent parameter value increases or decreases. The normalized forward sensitivity index methods is one amongst many available methods. This helps classifying the parameters with respect to their impact on the HIV prevalence and schedule control strategy accordingly. We shall use parameters values in Table 2 to compute the magnitude of each index. From [18], the normalized forward sensitivity indices of $\mathcal{R}_0$ with respect to each parameters are presented as follows:

$$\frac{c}{\mathcal{R}_0}\frac{\partial \mathcal{R}_0}{\partial c} = 1, \qquad \frac{\eta_2}{\mathcal{R}_0}\frac{\partial \mathcal{R}_0}{\partial \eta_2} = 0.81, \qquad \frac{\eta_1}{\mathcal{R}_0}\frac{\partial \mathcal{R}_0}{\partial \eta_1} = 0.077,$$

Table 2: Table of parameter values and their description

Parameter	Description	Value(yr^{-1})	Source
π	Recruitment rate	1,084,397	[19]
γ	PrEP awareness level	$0.72/[0, 0.99]$	[9]
σ	PrEP efficacy level	$0.85/[0, 0.99]$	[13]
μ	Natural death rate	0.0163	[19]
ρ_1	Progression rate from I class to A class	0.0740	[19]
ρ_2	Progression rate from I_p class to A class	0.060	Assumed
δ	Disease induced death rate	0.3190	[19]
η_1	Transmission rate per act with I_p individual	0.0219	[13]
η_2	Transmission rate per act with A individual	1.240	Assumed
c	Average per act transmission	2	Assumed

$$\begin{aligned} \frac{\sigma}{\mathcal{R}_0}\frac{\partial \mathcal{R}_0}{\partial \sigma} &= -3.94, \quad \frac{\delta}{\mathcal{R}_0}\frac{\partial \mathcal{R}_0}{\partial \delta} = -0.77, \quad \frac{\gamma}{\mathcal{R}_0}\frac{\partial \mathcal{R}_0}{\partial \gamma} = -0.45, \\ \frac{\rho_1}{\mathcal{R}_0}\frac{\partial \mathcal{R}_0}{\partial \rho_1} &= -0.081, \quad \frac{\rho_2}{\mathcal{R}_0}\frac{\partial \mathcal{R}_0}{\partial \rho_2} = -0.018, \quad \frac{\mu}{\mathcal{R}_0}\frac{\partial \mathcal{R}_0}{\partial \mu} = -0.13. \end{aligned}$$

The parameters with positive sensitivity index will increase the magnitude of $\mathcal{R}_0$ when their value increases, whereas parameters with negative sensitive index will decrease the magnitude of $\mathcal{R}_0$ when their value increases. Thus, it follows that an increase in the values of γ, σ, ρ_1, ρ_2, μ, and δ will lead to a decrease in value of $\mathcal{R}_0$ while an increase in the values of c, η_1 and η_2 will lead to an increase in the value of $\mathcal{R}_0$. However, for human ethical principle, increase purposely the natural mortality rate (μ), the rate of death related to AIDS (δ), and the progression rates of infected individuals to AIDS (ρ_1 and ρ_2) in order to decrease the value of $\mathcal{R}_0$ is not scientifically recommended. It therefore follows that the PrEP efficacy level σ is the most sensitivity parameter, followed by the proportion of individuals on PrEP use γ, then contact rates c, η_2, and η_1, on the infection dynamics. These results highlight the importance of PrEP awareness and PrEP efficacy level in reducing HIV infection spread in a community.

4.2.3. Contour plots of $\mathcal{R}_0$

The simulation result of $\mathcal{R}_0$ as function of γ and σ in form of contour plots in Figure 2 gives more information about the different proportion of γ and σ for an effective HIV incidence reduction. The simulation indicates that if at least 32% of the susceptible individuals (at risk of HIV infection) in the study community are enrolled in a consistence PrEP use while the PrEP efficacy level is ranged between 85–100%, then new HIV infections will be effectively controlled; which may further leads to a substantial eradication of the disease in the community.

4.3. Model equilibrium points

The system (2)-(6) has two equilibrium points, the disease free equilibrium (DFE) point E_0 and the endemic equilibrium point $\bar{E}$, which are obtained by equating the right-hand

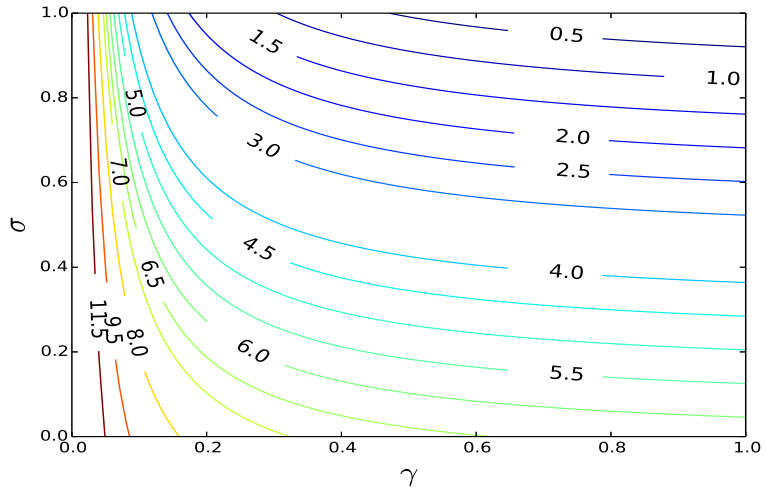

Figure 2: Simulation of the basic reproduction ratio $\mathcal{R}_0$ as function of the control parameters γ and σ in form of contour plots using parameters values in Table 2.

side of system (2)-(6) to zero. The DFE point is given by

$$E_0 = \left(\frac{\kappa\pi}{\mu}, \frac{(1-\kappa)\pi}{\mu}, 0, 0, 0\right), \tag{20}$$

and the endemic equilibrium point given by

$$\bar{E} = (\bar{S}, \bar{S}_p, \bar{I}, \bar{I}_p, \bar{A}), \tag{21}$$

where

$$\begin{aligned}
\bar{S} &= \frac{\pi}{\gamma + (1-\gamma)\lambda^* + \mu}, \\
\bar{S}_p &= \frac{\gamma\pi}{\big(\mu + (1-\sigma)\lambda^*\big)\big(\gamma + (1-\gamma)\lambda^* + \mu\big)}, \\
\bar{I} &= \frac{(1-\gamma)\lambda^*\pi}{\big(\rho_1 + \mu\big)\big(\gamma + (1-\gamma)\lambda^* + \mu\big)}, \\
\bar{I}_p &= \frac{(1-\sigma)\lambda^*\gamma\pi}{\big(\rho_2 + \mu\big)\big(\gamma + (1-\gamma)\lambda^* + \mu\big)\big(\mu + (1-\sigma)\lambda^*\big)}, \\
\bar{A} &= \frac{\lambda^*\pi}{\big(\gamma + (1-\gamma)\lambda^* + \mu\big)\big(\mu + \delta\big)}\left(\frac{\rho_1(1-\gamma)}{(\rho_1+\mu)} + \frac{\rho_2\gamma(1-\sigma)}{(\rho_2+\mu)(\mu + (1-\sigma)\lambda^*)}\right),
\end{aligned}$$

where λ^* is a positive solution to the quadratic equation

$$\lambda^{*2} - a_1\lambda^* + a_0 = 0, \tag{22}$$

where

$$\begin{aligned}
a_1 &= \frac{\delta\rho_1\mu(1-\gamma) + \rho_2\delta(\rho_1+\mu)}{(\mu+\rho_1+\delta)} + \frac{\mathcal{R}_1(\rho_1+\mu)(\mu+\delta)(1-\sigma)}{(1-\gamma)(\mu+\rho_1+\delta)}, \\
a_0 &= \frac{(\mu+\gamma)(\mu+\delta)(\rho_1+\mu)}{(1-\gamma)(1-\sigma)(\mu+\rho_1+\delta)}\left(1-\mathcal{R}_0\right).
\end{aligned}$$

The quadratic equation (22) has a unique positive real solution $\lambda^* > 0$ when $a_0 < 0$, that is $\mathcal{R}_0 > 1$. Thus $\lambda^* > 0$ corresponds to a unique endemic equilibrium point. Hence, we state the following:

Theorem 2. *The endemic equilibrium point of model (2)-(6) exists and is unique whenever* $\mathcal{R}_0 > 1$.

4.4. Stability analysis of the equilibrium points

Theorem 3. *The disease free equilibrium point of model (2)-(6) is globally asymptotically stable when* $\mathcal{R}_0 < 1$.

Proof. Following Van den Driessche and Watmough's technique [15], it suffices to consider the stability of the matrix $F - V$ where

$$\begin{aligned} F - V &= \begin{pmatrix} c\phi_1 - (\rho_1 + \mu) & c\eta_1\phi_1 & c\eta_2\phi_1 \\ c\phi_2 & c\eta_1\phi_2 - (\rho_2 + \mu) & c\eta_2\phi_2 \\ \rho_1 & \rho_2 & -(\mu + \delta) \end{pmatrix}, \\ \phi_1 &= (1-\gamma)\kappa, \quad \phi_2 = (1-\sigma)(1-\kappa). \end{aligned}$$

The eigenvalues of the matrix $F - V$ are roots of the characteristic equation

$$\lambda^3 + b_2\lambda^2 + b_1\lambda + b_0 = 0 \tag{23}$$

where

$$\begin{aligned} b_2 &= (\delta + \mu) + (\rho_1 + 2\mu + \rho_2)(1 - \mathcal{R}_0) + (\rho_1 + \mu)(1-\kappa)\mathcal{R}_2 + (\rho_2 + \mu)\kappa\mathcal{R}_1 \\ &+ \frac{\eta_2(\kappa\rho_1 + (1-\kappa)\rho_2)}{\mu + \delta}, \\ b_1 &= [(\mu + \rho_1)(\mu + \rho_2) + (\mu + \delta)(\rho_1 + \rho_2 + 2\mu)](1 - \mathcal{R}_0) \\ &+ (\mu + \delta)(\mu + \rho_1)(1-\kappa)\mathcal{R}_2 + (\mu + \delta)(\mu + \rho_2)\kappa\mathcal{R}_1 \\ &+ \frac{c\kappa(1-\gamma)\rho_1\eta_2(\rho_2 + \mu)}{(\mu + \delta)} + \frac{c(1-\kappa)(1-\sigma)\rho_2\eta_2(\rho_1 + \mu)}{(\mu + \delta)}, \\ b_0 &= (\mu + \delta)(\mu + \rho_1)(\mu + \rho_2)(1 - \mathcal{R}_0). \end{aligned}$$

Clearly b_0, b_1, b_2, and $b_1b_2 - b_0$ given by

$$b_1b_2 - b_0 = (\mu + \delta)C_1 + C_2C_1 + C_2(\mu + \rho_1)(\mu + \rho_2)(1 - \mathcal{R}_0),$$

where

$$\begin{aligned} C_2 &= (\rho_1 + 2\mu + \rho_2)(1 - \mathcal{R}_0) + (\rho_1 + \mu)(1-\kappa)\mathcal{R}_2 + (\rho_2 + \mu)\kappa\mathcal{R}_1 \\ &+ \frac{\eta_2(\kappa\rho_1 + (1-\kappa)\rho_2)}{\mu + \delta}, \\ C_1 &= (\mu + \delta)(\rho_1 + \rho_2 + 2\mu)(1 - \mathcal{R}_0) + (\mu + \delta)(\mu + \rho_1)(1-\kappa)\mathcal{R}_2 \\ &+ (\mu + \delta)(\mu + \rho_2)\kappa\mathcal{R}_1 + \frac{c\eta_2}{(\mu + \delta)}\left(\rho_1\phi_1(\rho_2 + \mu) + \rho_2\phi_2(\rho_1 + \mu)\right). \end{aligned}$$

are positive whenever $\mathcal{R}_0 < 1$. The Routh-Hurwitz criterion for stability [16] is satisfied when $\mathcal{R}_0 < 1$. This means that all the eigenvalues of the matrix $F-V$ are either negative or have negative real parts whenever $\mathcal{R}_0 < 1$. The local stability of the disease free equilibrium is therefore ensured. Nevertheless, this might not hold when one varies the initial conditions, otherwise the DFE is globally asymptotically stable.

To guarantee the global stability of the DFE point, we follow Castillo–Chavez *et al* technique in [17] to re-write system (2)-(6) in the form

$$\dot{X} = F(X,Y), \tag{24}$$
$$\dot{Y} = H(X,Y), \quad H(X,\mathbf{0}) = \mathbf{0}, \tag{25}$$

where the components of the vector $X = (S, S_p) \in \mathbb{R}^2_+$ denote the uninfected compartment and the components of the vector $Y = (I, I_p, A) \in \mathbb{R}^3_+$ denote the infected compartments. Thus, the DFE becomes $E_0 = (X^0, \mathbf{0})$ where

$$X^0 = (S^0, S_p^0) = \left(\frac{\pi\kappa}{\mu}, \frac{(1-\kappa)\pi}{\mu}\right). \tag{26}$$

The global stability property of the DFE is achieved when the following two conditions are satisfied:

$$\begin{aligned}
&\mathbf{H}_1 : \text{For} \quad \dot{X}(t) = F(X^0, \mathbf{0}),\ X^0 \text{ is globally asymptotically stable.}\\
&\mathbf{H}_2 : H(X,Y) = BY - \hat{H}(X,Y), \quad \hat{H}(X,Y) \geq 0 \quad \text{for} \quad (X,Y) \in \Omega_m,\\
&\text{where} \quad B = \frac{\partial H}{\partial Y}(X^0, 0).
\end{aligned}$$

From model (2)-(6), it follows that

$$B = \begin{pmatrix} c\phi_1 - (\rho_1 + \mu) & c\eta_1\phi_1 & c\eta_2\phi_1 \\ c\phi_2 & c\eta_1\phi_2 - (\rho_2 + \mu) & c\eta_2\phi_2 \\ \rho_1 & \rho_2 & -(\mu + \delta) \end{pmatrix},$$

$$F(X^0, \mathbf{0}) = \begin{pmatrix} \pi - (\mu + \gamma)S^0 - \alpha S_p^0 \\ \gamma S^0 - (\mu + \alpha)S_p^0 \end{pmatrix}, \quad \text{and}$$

$$\hat{H}(X,Y) = \begin{pmatrix} \hat{H}_1 \\ \hat{H}_2 \\ \hat{H}_3 \\ \hat{H}_4 \\ \hat{H}_5 \end{pmatrix} = \begin{pmatrix} (1-\gamma)(cI + c\eta_1 I_p + c\eta_2 A)\left(\kappa - \frac{S}{N}\right) \\ (1-\sigma)(cI + c\eta_1 I_p + c\eta_2 A)\left(1 - \kappa - \frac{S_p}{N}\right) \\ 0 \\ 0 \\ 0 \end{pmatrix}.$$

To prove condition $\mathbf{H}_1$, we observe that $\lim_{t\to\infty} X(t) = X^0$; thus X^0 is globally stable. That means $X(t)$ converges to X^0, independently from the initial conditions.

To prove condition $\mathbf{H}_2$, we require that $\hat{H}(X,Y) \geq 0$ that is $\hat{H}_1 \geq 0$ and $\hat{H}_2 \geq 0$. We proceed using a proof by contradiction, we assume that $\hat{H}_1 < 0$ and $\hat{H}_2 < 0$. This implies that

$$\kappa < \frac{S}{N} \qquad \text{and} \qquad 1-\kappa < \frac{S_p}{N}. \tag{27}$$

Adding both inequalities in (27), we obtain

$$1 < \frac{S+S_p}{N}, \quad \text{that is} \quad N < S + S_p, \tag{28}$$

which is a contradiction to the fact that $S + S_p \leq N$. Therefore $\hat{H}_1 \geq 0$ and $\hat{H}_2 \geq 0$. This guarantee the global stability of the DFE.
In summary, we note that independently of the given initial conditions, the DFE point will (globally asymptotically) remain stable whenever $\mathcal{R}_0 < 1$. In epidemiological meaning, this suggests that the HIV infection dynamic will remain under check or will be effectively controlled once the infection threshold magnitude is kept under unity.

Theorem 4. *The endemic equilibrium point of model (2)-(6) is globally asymptotically stable when* $\mathcal{R}_0 > 1$.

The proofs of Theorems 3 and 4 are standard, so omitted.

Proof. To analyse the local stability of the endemic point of model (2)–(6), we use centre manifold theory [17] by introducing the new variables $x_1 = S$, $x_2 = S_p$, $x_3 = I$, $x_4 = I_p$, $x_5 = A$ so that system (2)-(6) becomes

$$\begin{aligned}
\dot{x}_1 &= \pi - \gamma x_1 - (1-\gamma)\frac{c(x_3+\eta_1 x_4+\eta_2 x_5)x_1}{x_1+x_2+x_3+x_4+x_5} - \mu x_1, && (29)\\
\dot{x}_2 &= \gamma x_1 - (1-\sigma)\frac{c(x_3+\eta_1 x_4+\eta_2 x_5)x_2}{x_1+x_2+x_3+x_4+x_5} - \mu x_2, && (30)\\
\dot{x}_3 &= (1-\gamma)\frac{c(x_3+\eta_1 x_4+\eta_2 x_5)x_1}{x_1+x_2+x_3+x_4+x_5} - (\rho_1+\mu)x_3, && (31)\\
\dot{x}_4 &= (1-\sigma)\frac{c(x_3+\eta_1 x_4+\eta_2 x_5)x_2}{x_1+x_2+x_3+x_4+x_5} - (\rho_2+\mu)x_4, && (32)\\
\dot{x}_5 &= \rho_1 x_3 + \rho_2 x_4 - (\mu+\delta)x_5. && (33)
\end{aligned}$$

Considering c as the bifurcation parameter when $\mathcal{R}_0 = 1$ and solving for c, we obtain

$$c = c^* = \frac{(\mu+\gamma)(\mu+\delta)(\rho_2+\mu)(\rho_1+\mu)}{\mu(1-\gamma)((\mu+\delta)+\eta_2\rho_1)(\mu+\rho_2)+\gamma(1-\sigma)(\eta_1(\mu+\delta)+\eta_2\rho_2)(\mu+\rho_1)}.$$

The Jacobian matrix of the system of equations (29)-(33) evaluated at the DFE E_0 with $c = c^*$ is

$$M^* = \begin{pmatrix}
-\mu-\gamma & 0 & -c^*\phi_1 & -c^*\eta_1\phi_1 & -c^*\eta_2\phi_1 \\
\gamma & -\mu & -c^*\phi_2 & -c^*\eta_1\phi_2 & -c^*\eta_2\phi_2 \\
0 & 0 & c^*\phi_1-\rho_1-\mu & c^*\eta_1\phi_1 & c^*\eta_2\phi_1 \\
0 & 0 & c^*\phi_2 & c^*\eta_1\phi_2-\rho_2-\mu & c^*\eta_2\phi_2 \\
0 & 0 & \rho_1 & \rho_2 & -(\mu+\delta)
\end{pmatrix}.$$

It is easy to see that zero is a simple eigenvalue of the Jacobian matrix M^*. Thus, one can apply the centre manifold theory to determine the local stability of the endemic equilibrium point $\bar{E}$. The right eigenvector associated with the zero eigenvalue of the matrix M^* is given by

$$Y = (y_1, y_2, y_3, y_4, y_5)^\top,$$

where

$$\begin{aligned}
y_1 &= -\frac{\kappa(\mu+\rho_1)}{\mu},\\
y_2 &= -\frac{(\mu+\rho_1)(1-\kappa)(\kappa(1-\sigma)+(1-\gamma))}{\mu\kappa(1-\sigma)},\\
y_3 &= 1,\\
y_4 &= \frac{(1-\kappa)(1-\sigma)(\rho_1+\mu)}{\kappa(1-\gamma)(\rho_2+\mu)},\\
y_5 &= \frac{\rho_1}{\delta+\mu}+\frac{\rho_2}{\delta+\mu}\frac{(1-\kappa)(1-\sigma)(\rho_1+\mu)}{\kappa(1-\gamma)(\rho_2+\mu)}.
\end{aligned}$$

The left eigenvector associated with the zero eigenvalue of M^* is given by

$$Z = (z_1, z_2, z_3, z_4, z_5)^\top,$$

where

$$\begin{aligned}
z_1 &= 0,\\
z_2 &= 0,\\
z_3 &= 1,\\
z_4 &= \frac{(1-\gamma)\mathcal{R}_2}{(1-\sigma)\mathcal{R}_1},\\
z_5 &= \frac{c(1-\gamma)\eta_2}{(\mu+\delta)\mathcal{R}_1}.
\end{aligned}$$

To compute the bifurcation coefficients Υ_a and Υ_b defined in [17], we reconsider system (29)-(33) to be in form $\frac{dX}{dt} = f = (f_1, f_2, f_3, f_4, f_5)^\top$, where $X = (x_1, x_2, x_3, x_4, x_5)^\top$ so that

$$\begin{aligned}
\Upsilon_a &= \sum_{i,j,k=1}^{5} z_k y_i y_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(E_0, c^*),\\
\Upsilon_b &= \sum_{i,j,k=1}^{5} z_k y_i \frac{\partial^2 f_k}{\partial x_i \partial c^*}(E_0, c^*).
\end{aligned}$$

The coefficient Υ_a is thus obtained from the following non-vanishing partial derivatives

$$
\begin{aligned}
\frac{\partial^2 f_3}{\partial x_3^2} &= -2\alpha\kappa, \quad \frac{\partial^2 f_3}{\partial x_3 \partial x_4} = -(1+\eta_1)\alpha\kappa, \quad \frac{\partial^2 f_3}{\partial x_3 \partial x_5} = -(1+\eta_2)\alpha\kappa, \quad \frac{\partial^2 f_3}{\partial x_5^2} = -2\eta_2\alpha\kappa, \\
\frac{\partial^2 f_3}{\partial x_4^2} &= -2\eta_1\alpha\kappa, \quad \frac{\partial^2 f_3}{\partial x_4 \partial x_5} = -(\eta_1+\eta_2)\alpha\kappa, \quad \frac{\partial^2 f_4}{\partial x_3 \partial x4} = -(1+\eta_1)\beta(1-\kappa), \\
\frac{\partial^2 f_4}{\partial x_5^2} &= -2\eta_2\beta(1-\kappa), \quad \frac{\partial^2 f_4}{\partial x_4 \partial x_5} = -(\eta_1+\eta_2)\beta(1-\kappa), \quad \frac{\partial^2 f_4}{\partial x_3^2} = -2\beta(1-\kappa), \\
\frac{\partial^2 f_4}{\partial x_4^2} &= -2\eta_1\beta(1-\kappa), \quad \frac{\partial^2 f_4}{\partial x_3 \partial x_5} = -(1+\eta_2)\beta(1-\kappa),
\end{aligned}
$$

so that

$$
\Upsilon_a = -\frac{2\mu\alpha}{\kappa\mathcal{R}_1}\Big(1+\eta_1 y_4^2+\eta_2 y_5^2+(1+\eta_1)y_4+(1+\eta_2)y_5+(\eta_1+\eta_2)y_4y_5\Big) < 0.
$$

The coefficient Υ_b is obtained from the following non-vanishing partial derivatives

$$
\begin{aligned}
\frac{\partial^2 f_4}{\partial x_5 \partial c^*} &= (1-\kappa)(1-\sigma)\eta_2, \frac{\partial^2 f_3}{\partial x_4 \partial c^*} = \kappa(1-\gamma)\eta_1, \frac{\partial^2 f_3}{\partial x_5 \partial c^*} = \kappa(1-\gamma)\eta_2, \\
\frac{\partial^2 f_4}{\partial x_3 \partial c^*} &= (1-\kappa)(1-\sigma), \frac{\partial^2 f_4}{\partial x_4 \partial c^*} = (1-\kappa)(1-\sigma)\eta_1, \frac{\partial^2 f_3}{\partial x_3 \partial c^*} = \kappa(1-\gamma),
\end{aligned}
$$

so that

$$
\Upsilon_b = \frac{(1-\gamma)(1+\eta_1 y_4+\eta_2 y_5)}{\mathcal{R}_1} > 0.
$$

The bifurcation coefficients $\Upsilon_a < 0$ and $\Upsilon_b > 0$, the endemic equilibrium point is therefore locally asymptotically stable.

In light of what precedes, it follows that around the bifurcation point $\mathcal{R}_0 = 1$, the infection dynamics undergoes an exchange of stability, that is, before the bifurcation point, that is when $\mathcal{R}_0 < 1$, the disease free equilibrium point is locally asymptotically stable and after the bifurcation point, that is when $\mathcal{R}_0 > 1$, the DFE point becomes unstable and the endemic equilibrium point is locally asymptotically stable. The model therefore exhibits a transcritical bifurcation which is a supercritical bifurcation at $\mathcal{R}_0 = 1$. Moreover, in view of the uniqueness, the existence and the local stability conditions of the endemic equilibrium point obtained from Theorems 1 and 3, it follows that the endemic equilibrium point is globally asymptotically stable for $\mathcal{R}_0 > 1$.

5. Numerical simulations

In this section, we carry out numerical simulations using Python programming language. We shall determine the initial conditions of the PrEP model and estimate the parameter

values based on the HIV report from South Africa [19]. We will use initial conditions and parameter values to investigate the benefits from different possible PrEP intervention strategies. The results from the simulations based on the strategies will be used to find the best strategies that are viable for effective PrEP administration and possible HIV/AIDS burden reduction.

5.1. Parameter estimation

We are guided by the recent South Africa national report on HIV burden [19] for estimation of some the parameters not found in literature. We shall also use the report to determine the initial conditions based on the South Africa population statistics. People who qualify for PrEP use are sexually active and hence from the report we consider the population of individuals aged between 15 and 49 years. The population of individuals at risk of HIV between 15 to 49 years from the report was 28,907,999. This gives the initial condition for the susceptible population as $S(0) = 28,907,999$. Individuals living with HIV were 5.51 millions of whom 16.8% are aged between 15 and 49 years; this gives $I(0) = 925,680$. Since, apparently, there is no use of PrEP in the population, we assume that $S_p(0) = I_p(0) = 0$. The data does not distinguish between individuals living with HIV from those living with AIDS. Thus the impact of infectious and AIDS individuals will be judged from the effects of $I(0)$. This leads us to assume that $A(0) = 0$.

From the report [19], 1,084,397 individuals at risk aged between 15 to 49 years migrated into the population per year. The individuals join the non-PrEP susceptible individuals. This gives $\pi = 1,084,397$. The current life expectancy for South Africa is 59.1 years for males and 63.1 years for women. We take the life expectancy to be between 59.1 to 63.1 years. The natural death rate is then defined as the reciprocal of the life expectancy. Hence, $\mu \in (0.0158, 0.0169)$. For our numerical simulations, we considered μ to be the midpoint of the range so that $\mu = 0.0163$, which translates to a life expectancy of 61.10 years. In addition 31.9% of the individuals living with HIV were reported to have died of AIDS per year. This yields $\delta = 0.319$. On average, it was reported that an individual not on any treatment takes between 10.5 to 13.5 years to develop AIDS. The rate of progression from infectious HIV status to AIDS status is $1/\rho_1$ so that $\rho_1 \in (0.0740, 0.0952)$; we shall take $\rho_1 = 0.0740$. We assume that, unlike the non-PrEP infected individuals, the PrEP infected individuals (due to the PrEP drugs concentration in their blood) might take more years before developing full blown, i.e. $\rho_2 < \rho_1$. We take $\rho_2 = 0.060$, corresponding to 16.5 years. In [19], the authors estimated the HIV infection transmission rate from an infected individuals to a susceptible individual on Tenofovir gel by 0.0219. Without portraying a generality, we consider η_1 to be the same, i.e $\eta_1 = 0.0219$. As early considered $\eta_1 < 1 < \eta_2$, we assume that $\eta_2 = 1.240$. The parameters values are presented in Table 2 with the corresponding sources.

A study in [9] analysing the impact of Tenofovir gel as PrEP on HIV considered the use of PrEP efficacy below 50% to have low HIV infection prevention and the efficacy above 50% to have high HIV infection prevention. We use the same assumptions on

both PrEP use awareness and PrEP efficacy. We therefore consider four hypothetical scenarios associated with PrEP use and PrEP awareness and determine the one that works best. These are, as earlier on stated in section 1, (i) low PrEP use and low PrEP efficacy, (ii) low PrEP use and high PrEP efficacy, (iii) high PrEP use and low PrEP efficacy and (iv) high PrEP use and high PrEP efficacy. In our simulations $\gamma = \sigma = 0.35$ for low PrEP use and low PrEP efficacy and $\gamma = \sigma = 0.85$ for high PrEP use and high PrEP efficacy in view of characterization of low and high efficacy in [9]. While we acknowledge that any changes in the values of γ and σ may result in changes in the curves, the qualitative behaviour of the curves are maintained.

5.2. Simulations

The numerical simulation results for our model are represented in Figures 3(a)-(f). Figures 3(a)-(e) shows the efficacy of the four PrEP strategies on the state variables whilst Figure 3(f) shows the corresponding prevalence for each strategy.

Figure 3(a) shows an earlier decline in non-PrEP susceptibles at high risk of infection due PrEP use and PrEP efficacy. This change is associated with the increase in number of PrEP susceptibles . Unlike the other three PrEP strategies, which show a decline in numbers of PrEP susceptibles after the first five years, the strategy with high PrEP use and high PrEP efficacy demonstrate a steep increase of PrEP users over the study period (Figure 3(b)). We thus note that to maintain more people free of infection, the best strategy is to implement high PrEP use and high PrEP efficacy.

Application of this latter strategy predicts, in Figure 3(c), a great decrease in number of new HIV infections in the non-PrEP infectives population, which tends to zero. Moreover, in the PrEP infectives population, strategy with high PrEP use and low efficacy is shown, in Figure 3(d), to be the worst strategy. This is characterised by a switching dominance. This gives a warning on PrEP efficacy level if PrEP is to be delivered. Thus, we note that the worst strategy is administrating high PrEP use and low PrEP efficacy.

In Figure 3(e), simulation of the AIDS population is represented. We observe some switching dominance in the strategies for decreasing these populations. We note that the great decrease of AIDS population is tied to high PrEP use and high PrEP efficacy strategy. The simulation results of the prevalence, in Figure 3(f), of each strategy highlight the need of considering PrEP use and PrEP efficacy at high levels if HIV infection spread is to be effectively controlled.

Overall, we realize that the short term benefits in the use of PrEP are observed to come from low PrEP use with high PrEP efficacy, whilst the worst strategy comes from implementing high PrEP use and low PrEP efficacy. However, for a long run, the best benefit is realized on the high PrEP use and high efficacy, whilst the worst will come from low PrEP use and low PrEP efficacy.

Our numerical simulation results therefore suggest that the high PrEP use and high PrEP efficacy can best be used as a strategy to a certain limit but cannot sustain the

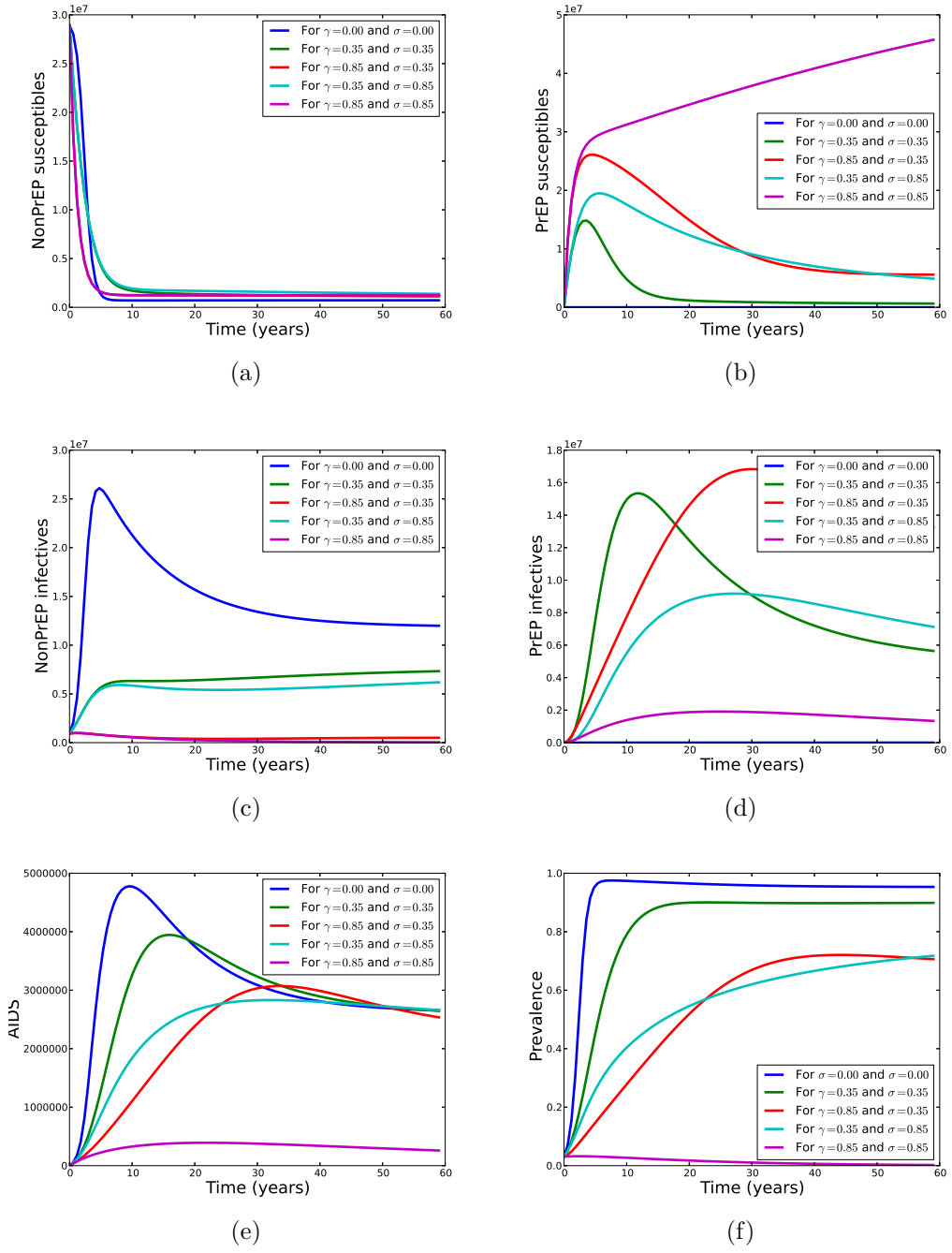

Figure 3: Time evolution of each sub-population defined showing the impact of PrEP use and PrEP efficacy at different levels.

reduction in HIV/AIDS burden on its own.

In Table 3, we give precise values of the reproduction ratios with the corresponding levels of PrEP strategies and risk reduction rate by comparing these strategies with the case where PrEP is not use at all.

Table 3: Reproduction ratios and PrEP risk reduction compared with no PrEP use case

Case	γ	σ	$\mathcal{R}_{fast}$	$\mathcal{R}_{slow}$	κ	$\mathcal{R}_0$	Risk reduction (%)
(a)	0.00	0.00	28.20	0.00	1.00	28.20	–
(b)	0.35	0.35	3.96	0.61	0.041	4.78	83%
(c)	0.85	0.35	4.07	0.079	0.017	4.15	85%
(d)	0.35	0.85	0.91	0.81	0.041	1.73	94%
(e)	0.85	0.85	0.94	0.079	0.017	1.03	96%
(f)	0.86	0.86	0.87	0.07	0.017	0.95	97%

6. Discussion

We analysed an HIV model which captured the dynamics of PrEP use and PrEP efficacy to investigate the potential impact of possible strategies emanating from PrEP use and PrEP efficacy. Analytical results revealed that the model incorporating PrEP was a parameter connected model. This means that the model can be subdivided into two sub-models so that the reproduction ratio of the original model can be expressed as a linear combination of the reproduction ratios of the two sub-models. One sub-model was a non-PrEP users model and the other was the PrEP users model. The parameter connecting the two reproduction ratios was classified as slow-fast parameter. This parameter was important in our model in sense that it made possible for one to trace at any time t whether it is the non-PrEP users or PrEP users dominating the dynamics of HIV infection. Thus the two reproduction ratios were classified as either slow reproduction ratios or fast reproduction ratios. Our results revealed that the low PrEP use and low PrEP efficacy, the low PrEP use and high PrEP efficacy and the high PrEP use and high PrEP efficacy strategies were dominated by the fast reproduction ratio associated with the non-PrEP users. The high PrEP use and low PrEP efficacy strategy is the only strategy whose dynamics are controlled by the fast reproduction ratio associated with the PrEP users (see Table 3). Our results seem to suggest that even in the presence of PrEP, the non-PrEP proportion of the population can still dominate the HIV infection dynamics.

Numerical simulations on the four strategies showed that the high PrEP use and high PrEP efficacy strategy reduces HIV prevalence better than any other strategies whilst the low PrEP use and low PrEP efficacy strategy was the worst strategy. In the other scenarios (except that of the high PrEP use and high PrEP efficacy), the prevalence gradually increases; this implies the following: either the PrEP use awareness and PrEP efficacy should be improved if not made perfect or PrEP alone as a mono-strategy cannot be used to manage the HIV burden for a long time. Our results also suggested that the strategies using high PrEP efficacy with low PrEP use seem to have better benefits than the one using high awareness with low efficacy. In addition, in most of the strategies considered, the basic reproduction ratio was above unity although that was reduced significantly compared with the case where PrEP is not use at all. The reproduction ratio could only be reduced to below unity whenever the PrEP use and PrEP efficacy were at least 85% percent. The study in [13] reported that PrEP efficacy

of at least 80 percent was able to reduce the basic reproduction ratio below unity. Our results in this study with parameter values from the South African HIV statistics [19] are in agreement with the result in [13].

Our study presented some of the benefits that come as a result of PrEP use and its efficacy. We note that the benefits presented here may be affected by several factors. These include drug resistance where individuals can develop primary and secondary resistance to PrEP ARVs and development of side effects. PrEP use may also lead to risky sexual behavior because people may feel protected against HIV infection. The increase in risky sexual behaviour may have negative effects especially if the low PrEP efficacy is part of the strategy. Thus PrEP administration needs to be implemented together with other forms of intervention such as effective use of condoms and post infection intervention methods such as the use of HAART and home-based care. For effective implementation of PrEP programs, care should also be taken to minimize costs of PrEP but maximizing the PrEP benefits.

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Chapter 3

Pre-exposure prophylaxis and antiretroviral treatment interventions with drug resistance

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Review

Pre-exposure prophylaxis and antiretroviral treatment interventions with drug resistance

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ABSTRACT

We introduce a model for HIV/AIDS which can be utilized to assess the impact of combining pre-exposure prophylaxis (PrEP) and antiretroviral drugs (ARVs) use interventions (incorporating drug resistance). Mathematical and numerical analyses are carried out to investigate the effects of the combined controls in the presence of PrEP drug resistance. Our results predict a significant decrease in the number of new HIV infections when PrEP and ARVs are concurrently implemented at high levels. The results also reveal that PrEP drug resistance has the potential to slow down or reverse the effects of PrEP, especially at low efficacy levels.

1. Introduction

HIV/AIDS infection has been an unbearable health burden for the human population across the world for decades and continues to cause massive loss of lives, especially in the resources-constrained countries. From the recent data of the World Health Organisation (WHO), an estimated 36.7 (34.0–39.8) million people were living with HIV, with 2.1 (1.8–2.4) million newly infected globally, and 1.1 million deaths due to HIV/AIDS disease in 2015 [1]. Effective prevention strategies and potent HIV cure medicines are imperatively needed even though many clinical trials and research studies have already been undertaken (and are still on ongoing) throughout the world. The situation has been exacerbated by the non-adherence to risky behavioural change interventions such as safe sexual practices, monogamy, and sterilisation of blood tools. This is especially prevalent in the young adults class and individuals with low literacy. Fortunately, antiretroviral drug (ARVs) use has helped in improving the life expectancy of already-infected individuals. Globally, 17 million people living with HIV were accessing antiretroviral therapy (ART) by December 2015, up from 15.8 million in June 2015 [1]. ART programmes have globally averted an estimated 7.8 million deaths between 2000 and 2014 [2]. Consistent and appropriate intake of the HIV life-saving antiretroviral drugs by infected individuals was also found to reduce the risk of infecting their sero-negative partners. ART has thus played a crucial role in the fight against HIV infection, especially in preventing mother-to-child transmission [3]. Prevention is the ideal and most effective strategy to significantly reduce the HIV burden. Of course, vaccination would be a very effective preventive strategy but, so far, no HIV vaccine is available.

On July 16, 2012, two ARVs namely Tenofovir and Truvada (a co-formulation of Emtricitabine and Tenofovir) were approved by the US Food and Drug Administration, for legal prescription by medical health experts, in the form of pre-exposure prophylaxis (PrEP) [4,5]. PrEP consists of administering the HIV drugs to uninfected individuals, particularly to those at high risk of infection. PrEP is not an HIV vaccine, but a new preventive approach. Several clinical trials (iPrEx, Partners, TDF2, Caprisa) were launched across America, Africa, and Asia, targeting sex workers, injecting drug users, men who have sex with men, transgender women, and heterosexual women to evaluate the biological safety and the effectiveness of the two recommended drugs. Results from these trials showed that both drugs were sufficiently potent to avert HIV infection through sexual intercourse. The iPrEx trial, on men who have sex with men (MSM) and transgender women who have sex with men, provided evidence that consistent daily oral Truvada intake reduced the risk of HIV infection by 44%. The Partners PrEP trial, results showed that the Tenofovir gel reduced the risk of infection by at least 62% and Truvada's protection ranged between 63% and 73% [6]. Results from animals' studies also confirmed the PrEP's usefulness by providing valuable information about PrEP effectiveness [7,8]. Thus, PrEP has become an ideal and promising preventive intervention for the HIV pandemic.

PrEP intervention studies have encountered various challenges and suffer from some limitations. These include devising an implementation strategy for effective PrEP awareness enabling max-

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imum enrolment of the targeted individuals, the efficacy level of PrEP drugs for optimal protection, and the PrEP drugs' resistance which results from PrEP use by already-infected individuals. Evidence has showed that maximum protection via PrEP for HIV infection depended on the percentage of the daily doses of PrEP drugs taken by an uninfected individual. If taken properly this reduced HIV incidence by 92% [9]. The adherence level of PrEP drugs is actually a result of the quality of the PrEP awareness campaign. The PrEP adherence level may thus be regarded as a measure of the PrEP awareness level.

The efficacy of drugs is generally an important factor in any health program roll out. Before Tenovofir and Truvada were introduced, Garcia–Lerma et al. [8,10] assessed PrEP efficacy levels through rhesus macaque models of simian human immunodeficiency virus infection. For the same purpose, Van Rompay et al. [11] looked into PrEP efficacy issue. Their results revealed that PrEP may be less protective against infection with drug-resistance viruses than against infection with wild-type viruses. Later, the FEM-PrEP trial with Truvada-based PrEP, in Kenya, and the VOICE trial with Tenofovir-based PrEP, in heterosexual African women, were discontinued due to the uncertainty of the drug protection. Thus PrEP efficacy levels should not be ignored when assessing PrEP effectiveness on HIV infection control. As a result, we include PrEP efficacy as one of the key control factors in this study.

PrEP drug resistance is thus a key factor that weakens the overall effectiveness of PrEP intervention. PrEP resistance emerges from two possible scenarios: (i) when an already-infected individual inadvertently begins taking PrEP or (ii) when an individual on PrEP acquires infection and continues taking the drug. Here, we will concentrate on the first scenario. This is due to the fact that this commonly occurs with individuals infected in the window period before PrEP enrolment and are unlikely to be revealed. Individuals willing to be on PrEP (or willing to renew a prescription) are actually recommended to go through a pre-randomized test before PrEP prescription. However, the available HIV antibody tests can not help in detecting infection during the window period [12,13]. This may compromise the effective control of HIV infection spread.

Various mathematical models [14–16] have been developed to investigate different aspects of PrEP. Some studies focussed on calibrating HIV incidence reduction by ARV therapy [17–19] . Smith et al. [20] investigated the impact of antiretroviral resistance on HIV infection control for the scenario where PrEP is to be used on a massive scale. Bhunu and Mushayabasa [21] assessed the impact of using antiretroviral drugs as pre-exposure vaccines. A common feature of these studies is that they only considered one control strategy (either PrEP or ARVs). We believe that it will be more beneficial to combine PrEP and ARV interventions in HIV control. We thus formulate an HIV/AIDS model using a system of nonlinear ordinary differential equations (ODEs), incorporating PrEP awareness level, PrEP efficacy, and ARV treatment coverage as key control factors. We also incorporate the impact of PrEP drug resistance with already-infected individuals on PrEP. In our model analysis, the PrEP awareness level will not be distinguished from PrEP adherence. In addition, we assumed that susceptible individuals who adhere to PrEP use will continuously be on PrEP over the study period.

2. Model formulation

The model describes HIV infection dynamics in a human population of density $N(t)$, where PrEP and ARV use are implemented. We subdivide the total population into seven sub-populations of individuals based on their infection status (susceptible/infected), their PrEP use status (on/not on), the period of infection (pre-infected/post-infected) when on PrEP, their post-infection care, and their infection stage (AIDS). The total population $N(t)$ is thus composed of susceptible individuals who either have never been aware of PrEP drug use for HIV prevention or are aware but are not convinced of the benefits of PrEP protection but are at substantial risk of HIV infection ($S(t)$), susceptible individuals on PrEP use ($S_p(t)$), infected non-PrEP users ($I(t)$), pre-infected individuals who developed drug resistance under PrEP use due to a false outcome of the pre-randomized test ($I_{p^-}(t)$), post-infected individuals due to PrEP protection failure ($I_p(t)$), infected individuals enrolled into ARV treatment programs $T(t)$, and infected individuals who developed full blown AIDS $A(t)$. Hence, at time $t \geq 0$, the total population is given by

$$N(t) = S(t) + S_p(t) + I(t) + I_p(t) + I_{p^-}(t) + T(t) + A(t). \tag{1}$$

All these individuals are considered sexually active and aged between 15 and 49 years. Thus, they are assumed to be mature enough to receive comprehensive HIV infection prevention/treatment education. HIV infection dynamics within the population is modelled based on the following assumptions: We assume that a proportion γ of susceptible individuals $S(t)$ is enrolled in a PrEP regimen, whilst the remaining proportion $(1-\gamma)$ indulge in behaviour associate with a high risk of HIV infection with no PrEP use at a rate λ, where λ denotes the force of infection given by

$$\lambda(t) = \frac{cI(t) + c\eta_1 I_p(t) + c\eta_2 I_{p^-}(t) + c\eta_3 T(t) + c\eta_4 A(t)}{N(t)}. \tag{2}$$

In Eq. (2), the coefficients η_i, $i = 1, \ldots, 4$, represent the transmission rates from the corresponding infected individual to a susceptible individual, while the coefficient c is the average number of unsafe sexual acts.We assume that the likelihood of a successful HIV infection transmission resulting from unsafe sexual contact between an infected PrEP user (I_p) and a typical susceptible individual is less than that of infected individual in $I_{p^-}(t)$ class, i.e $\eta_1 < \eta_2$ (This is due to the drug concentration in their blood plasma). Similarly, infected individuals on treatment are assumed to be least infectious whereas AIDS individuals are the most infectious. These assumptions translate to $\eta_3 < \eta_1 < \eta_2 < \eta_4$. PrEP is not 100% efficacious, so we assume that only a proportion σ of the susceptible individuals on PrEP use ($S_p(t)$) are protected from HIV infection. As a result, the remaining $(1-\sigma)S_p(t)$ individuals become infected at the rate λ. The parameter σ is hypothetically assumed to measure the average efficacy of the PrEP drugs. Of those who become infected under PrEP protection, a proportion θ, $0 < \theta < (1-\sigma)$, is recognized as being infected before PrEP intake. These infected individuals actually present PrEP drug resistance at the PrEP post-randomized test. Further, whether they have been on PrEP or not, individuals who are detected as HIV-positive at the post-randomized PrEP test are enrolled into an ART program to ensure that they do not spread the disease further. We assume that these individuals seek treatment at an average rate ϵ, $0 < \epsilon < 1$. Thus, infected individuals in the $I(t)$, $I_p(t)$, and $I_{p^-}(t)$ classes who enrol into treatment programs are moved to the $T(t)$ class, at rate $\epsilon\rho_i$, $i = 1, 2, 3$, while those who do not and develop AIDS are moved into the AIDS class, $A(t)$, at the rate $(1-\epsilon)\rho_i$, respectively. Here, ρ_1, ρ_2, and ρ_3 represent the progression rates of individuals out of the $I(t)$, $I_p(t)$, and $I_{p^-}(t)$ classes, respectively. We assume that individuals on ARV treatment progress to the AIDS class at the rate ρ_4 (and hence, we assume this is slowest progression rate). Owing to their reluctance for HIV infection prevention care, we assume that infected individuals in the $I(t)$ class may take more time to move to the treatment class $T(t)$, compared to infected individuals in the $I_p(t)$ class (for whom PrEP education continues to influence their decision to undergo treatment). Thus, $\frac{1}{\rho_2} < \frac{1}{\rho_1}$. We also assume that infected individuals in the $I_{p^-}(t)$ class will move to the treatment class the first before all other infected individuals. This translates to $\rho_3 > \rho_2 > \rho_1 > \rho_4$. All individuals experience natural death at the same rate μ, while AIDS individuals die from the

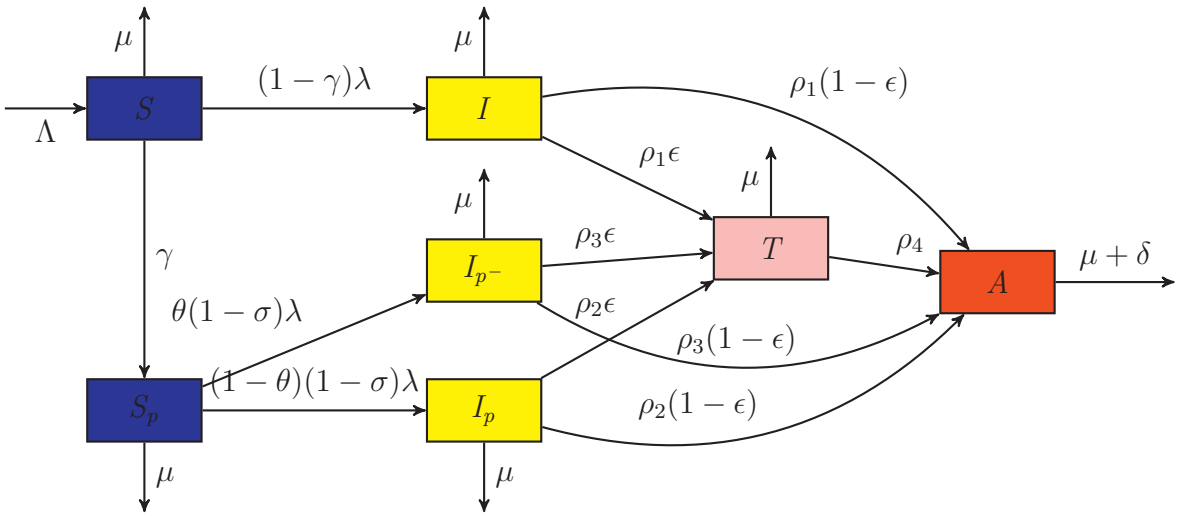


Fig. 1. The flow diagram of HIV infection dynamics between the sub-populations defined.

disease at a rate δ. Infection-free individuals are recruited into the population via the susceptible class $S(t)$ at a constant rate Λ. With these assumptions, we can schematically represent the movement of individuals in the seven sub-populations as indicated in Fig. 1. The mathematical analogue of the figure is given by the following system of nonlinear ordinary differential equations:

$$\dot{S} = \Lambda - \gamma S - (1-\gamma)\lambda S - \mu S, \tag{3}$$

$$\dot{S}_p = \gamma S - (1-\sigma)\lambda S_p - \mu S_p, \tag{4}$$

$$\dot{I} = (1-\gamma)\lambda S - (\rho_1+\mu)I, \tag{5}$$

$$\dot{I}_p = (1-\theta)(1-\sigma)\lambda S_p - (\rho_2+\mu)I_p, \tag{6}$$

$$\dot{I}_{p^-} = \theta(1-\sigma)\lambda S_p - (\mu+\rho_3)I_{p^-}, \tag{7}$$

$$\dot{T} = \rho_1\epsilon I + \rho_2\epsilon I_p + \rho_3\epsilon I_{p^-} - (\mu+\rho_4)T, \tag{8}$$

$$\dot{A} = \rho_1(1-\epsilon)I + \rho_2(1-\epsilon)I_p + \rho_3(1-\epsilon)I_{p^-} + \rho_4 T - (\mu+\delta)A, \tag{9}$$

with initial conditions $S(0)=S_0$, $S_p(0)=S_{p0}$, $I(0)=I_0$, $I_p(0)=I_{p0}$, $T(0)=T_0$, $I_{p^-}(0)=I_{p^-0}$, $A(0)=A_0$.

3. Model analysis

We can now analyse the HIV infection dynamics within the population using the system of Eqs. (3)–(9). In particular, we investigate the model's fundamental properties such as the biological feasible region, the epidemic threshold as well as the equilibrium points and their stability conditions, which are key to the understanding the infection dynamics and the impact of the control strategies used.

3.1. The positive invariant region

The state variables $S(t)$, $S_p(t)$, $I(t)$, $I_p(t)$, $I_{p^-}(t)$, $T(t)$, and $A(t)$ as defined in Table 1 represent human populations and the system of Eqs. (3)–(9) monitors the flow between the seven sub-populations. Hence, all the associated parameters are assumed to be non-negative. For biological reasons, we need to guarantee that all solutions of the system (3)–(9) are positive and will remain positive for all the time $t \geq 0$.

We re-write Eq. (3) as

$$\dot{S} \geq \Lambda - ((1-\gamma)\lambda + \gamma + \mu)S,$$

Table 1
Table of variables and their description.

Variables	Description
$S(t)$	Susceptible individuals non-PrEP users
$S_p(t)$	Susceptible individuals PrEP users
$I(t)$	Infected non-PrEP users
$I_p(t)$	Infected PrEP users
$I_{p^-}(t)$	Already-infected individuals on PrEP use
$T(t)$	Infected individuals on ARVs treatment
$A(t)$	AIDS individuals
$\lambda(t)$	Force of infection

so that

$$\frac{d}{dt}\left[S(t)\exp\left\{(\gamma+\mu)t + \int_0^t (1-\gamma)\lambda d\tau\right\}\right] \geq \Lambda \exp\left\{(\gamma+\mu)t + \int_0^t (1-\gamma)\lambda d\tau\right\}. \tag{10}$$

Integrating both sides of (10) gives

$$S(t)\exp\left\{(\gamma+\mu)t + \int_0^t (1-\gamma)\lambda d\tau\right\} - S(0) \geq \int_0^t \Lambda \exp\left\{(\gamma+\mu)z + \int_0^z (1-\gamma)\lambda d\tau\right\} dz,$$

which implies

$$S(t) \geq \left(\int_0^t \Lambda \exp\left\{(\gamma+\mu)z + \int_0^z (1-\gamma)\lambda d\tau\right\}\right) \times \left[\exp\left\{-(\gamma+\mu)t - \int_0^t (1-\gamma)\lambda d\tau\right\}\right] + S(0)\left[\exp\left\{-(\gamma+\mu)t - \int_0^t (1-\gamma)\lambda d\tau\right\}\right] > 0. \tag{11}$$

Result (11) indicates that the state variable $S(t)$ is non-negative provided that its initial value $S(0)$ is non-negative. The positiveness of the state variable $S(t)$ is therefore guaranteed.

Similarly, it can be shown that the state variables $S_p(t)$, $I(t)$, $I_p(t)$, $I_{p^-}(t)$, $T(t)$, and $A(t)$ are non-negative provided that their initial values $S_p(0)$, $I(0)$, $I_p(0)$, $I_{p^-}(0)$, $T(0)$ and $A(0)$ are non-negative, respectively.

Moreover, adding all the equations of system (3)–(9) gives

$$\dot{N}(t) \leq \Lambda - \mu N(t). \tag{12}$$

Solving (12), we obtain

$$N(t) \leq \frac{\Lambda}{\mu} + \left(N(0) - \frac{\Lambda}{\mu}\right)e^{-\mu t}, \tag{13}$$

from which, we note that $N(t)$ converges to $\frac{\Lambda}{\mu}$, as $t \to \infty$. This indicates that all solutions of system (3)–(9) are bounded above by $\frac{\Lambda}{\mu}$, in a positive region of $\mathbb{R}^7_+$. Hence, we define the set Ω, given by

$$\Omega = \left\{(S, S_p, I, I_p, I_{p^-}, T, A) \in \mathbb{R}^7_+ | S + S_p + I + I_p + I_{p^-} + T + A \leq \frac{\Lambda}{\mu}\right\}, \tag{14}$$

as the feasible and biologically meaningful region where the existence, positiveness, uniqueness, and continuity of the model solutions hold. We conclude that all solutions of system (3)–(9), starting with non-negative values in Ω, will remain non-negative in Ω, for all the time $t \geq 0$. We therefore claim that the region Ω is positively invariant under the flow induced by the model. We proceed to analyse the model in Ω.

3.2. Equilibrium points of the model and stability analysis

In this section, we compute the equilibrium points of the model and establish their stability conditions. The equilibrium points of the model indicate a situation of the infection dynamics within the population when no new infection or progression of individuals from one sub-population to another occur. In other words, at the equilibrium point, no change in the size of the sub-populations occur with the increase in time. Our model has two equilibrium points; the disease free equilibrium point and the endemic equilibrium point.

3.2.1. The disease free equilibrium point and stability analysis

In the absence of infection, that is, when $\lambda = 0$, the system (3)–(9) has a disease free equilibrium point (DFE) given by

$$\begin{aligned}\mathcal{E}^0 &= (S_0, S_{p0}, I_0, I_{p0}, I_{p^-0}, T_0, A_0)\\ &= \left(\frac{\Lambda}{(\mu+\gamma)}, \frac{\Lambda\gamma}{\mu(\mu+\gamma)}, 0, 0, 0, 0, 0\right).\end{aligned} \tag{15}$$

The stability conditions of the DFE point are explored using the control reproduction number [22,23], which is computed using the next generation operator method [24,25], given by

$$V^{-1} = \begin{pmatrix} \frac{1}{\rho_1+\mu} & 0 & 0 & 0 & 0 \\ 0 & \frac{1}{\rho_2+\mu} & 0 & 0 & 0 \\ 0 & 0 & \frac{1}{\rho_3+\mu} & 0 & 0 \\ \frac{\epsilon\rho_1}{(\rho_1+\mu)(\rho_4+\mu)} & \frac{\epsilon\rho_2}{(\rho_2+\mu)(\rho_4+\mu)} & \frac{\epsilon\rho_3}{(\rho_3+\mu)(\rho_4+\mu)} & \frac{1}{\rho_4+\mu} & 0 \\ \frac{\rho_1(\rho_4+\mu(1-\epsilon))}{(\rho_1+\mu)(\rho_4+\mu)(\delta+\mu)} & \frac{\rho_2(\rho_4+\mu(1-\epsilon))}{(\rho_2+\mu)(\rho_4+\mu)(\delta+\mu)} & \frac{\rho_3(\rho_4+\mu(1-\epsilon))}{(\rho_3+\mu)(\rho_4+\mu)(\delta+\mu)} & \frac{\rho_4}{(\rho_4+\mu)(\delta+\mu)} & \frac{1}{\delta+\mu} \end{pmatrix}$$

and

$$F = \begin{pmatrix} \frac{c(1-\gamma)\mu}{\gamma+\mu} & \frac{c(1-\gamma)\eta_1\mu}{\gamma+\mu} & \frac{c(1-\gamma)\eta_2\mu}{\gamma+\mu} & \frac{c(1-\gamma)\eta_3\mu}{\gamma+\mu} & \frac{c(1-\gamma)\eta_4\mu}{\gamma+\mu} \\ \frac{c(1-\sigma)(1-\theta)\gamma}{\gamma+\mu} & \frac{c(1-\sigma)\eta_1(1-\theta)\gamma}{\gamma+\mu} & \frac{c(1-\sigma)\eta_2(1-\theta)\gamma}{\gamma+\mu} & \frac{c(1-\sigma)\eta_3(1-\theta)\gamma}{\gamma+\mu} & \frac{c(1-\sigma)\eta_4(1-\theta)\gamma}{\gamma+\mu} \\ \frac{c(1-\sigma)\theta\gamma}{\gamma+\mu} & \frac{c(1-\sigma)\eta_1\theta\gamma}{\gamma+\mu} & \frac{c(1-\sigma)\eta_2\theta\gamma}{\gamma+\mu} & \frac{c(1-\sigma)\eta_3\theta\gamma}{\gamma+\mu} & \frac{c(1-\sigma)\eta_4\theta\gamma}{\gamma+\mu} \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix}.$$

$$\begin{aligned}\mathcal{R}_{pt} = &\frac{g_1(g_o + (\eta_3 h + g)\rho_1)}{(\rho_1+\mu)(\delta+\mu)} + \frac{g_2(\eta_1 g_o + (\eta_3\ h + g)\rho_2)}{(\rho_2+\mu)(\delta+\mu)}\\ &+ \frac{g_3(\eta_2 g_o + (\eta_3\ h + g)\rho_3)}{(\rho_3+\mu)(\delta+\mu)},\end{aligned} \tag{16}$$

where $g_o = (\rho_4+\mu)(\delta+\mu), g_1 = \frac{c(1-\gamma)\mu}{(\gamma+\mu)(\rho_4+\mu)}, g_2 = \frac{c(1-\theta)(1-\sigma)\gamma}{(\gamma+\mu)(\rho_4+\mu)}$, $g_3 = \frac{c\theta(1-\sigma)\gamma}{(\gamma+\mu)(\rho_4+\mu)}$, $g = \eta_4(\rho_4 + \mu(1-\epsilon))$, $h = \epsilon(\delta+\mu)$.

The control reproduction number $\mathcal{R}_{pt}$ is a threshold quantity which measures the ability of the infected individuals to give rise to secondary infections when a single infected individual is introduced into a purely susceptible population (where PrEP and ARV use programs are implemented). The parameter $\mathcal{R}_{pt}$ is one of the key thresholds used to understand the infection dynamics and the impact of the control strategies applied. The first term represents the contribution of the infected non-PrEP users, individuals on treatment and AIDS individuals through the infection route $I(t) \rightsquigarrow T(t) \rightsquigarrow A(t)$ in Fig. 1. The second term represents the contribution of infected individuals who were not protected by PrEP, those infected from the $I_p(t)$ class on treatment, and AIDS individuals through the infection route $I_p(t) \rightsquigarrow T(t) \rightsquigarrow A(t)$. The last term represents the contribution of the already-infected individuals exposed to PrEP use through the $I_{p^-}(t) \rightsquigarrow T(t) \rightsquigarrow A(t)$ route.

From Theorem 2 in [24], we claim that

Theorem 1. *The disease free equilibrium point of the model is locally asymptotically stable when $\mathcal{R}_{pt} < 1$ and unstable otherwise.*

Theorem 1 simply indicates that if the size of the seven sub-populations correspond to the coordinates of the DFE point, the infection can be eradicated from the population under the constraint $\mathcal{R}_{pt} < 1$. In addition, Theorem 1 indicates that, under a small influx of infected individuals within the pure susceptible population, HIV infection will not generate large outbreaks, and will die out in time provided that $\mathcal{R}_{pt} < 1$. However, the infection control may not be guaranteed for a large influx of infected individuals into the purely susceptible population. To explore conditions under which the eradication of the infection is independent of the size of the infected populations that flow into the population, we investigate the global stability of the DFE point.

We use the matrix-theoretic method [26] to analyse the global stability of the DFE point by defining a function $\mathcal{L}_o \in \mathcal{C}^1[\Omega, \mathbb{R}]$, given by

$$\mathcal{L}_o = w^\top V^{-1} X, \tag{17}$$

where $X = [I, I_p, I_{p^-}, T, A]^\top$ is a vector of populations from the infected compartments and $w^\top$ is the left eigenvector corresponding to the eigenvalue $\rho(V^{-1}F) = \rho(FV^{-1}) = \mathcal{R}_{pt}$ of matrix $V^{-1}F$, where

We claim that $\mathcal{L}_o$ is a Lyapunov function provided that $\mathcal{R}_{pt} < 1$. That is, the time derivative of $\mathcal{L}_o$ is negative definite when $\mathcal{R}_{pt} < 1$. We show this as follows: The time derivative $\frac{d\mathcal{L}_o}{dt}$ of $\mathcal{L}_o$ along the solutions of system (3)–(9) is given by

$$\begin{aligned}\frac{d\mathcal{L}_o}{dt} &= w^\top V^{-1}\frac{dX}{dt}\\ &= w^\top V^{-1}[(F-V)X-R]\\ &= w^\top V^{-1}(F-V)X - w^\top V^{-1}R\\ &= (\mathcal{R}_{pt}-1)w^\top X - w^\top V^{-1}R\\ &= -w^\top V^{-1}R - (1-\mathcal{R}_{pt})w^\top X,\end{aligned}$$

where

$$R=\begin{pmatrix}(1-\gamma)\frac{\lambda}{N}\left(\frac{\mu}{\gamma+\mu}-\frac{S}{N}\right)\\ (1-\sigma)(1-\theta)\frac{\lambda}{N}\left(\frac{\gamma}{\gamma+\mu}-\frac{S_p}{N}\right)\\ (1-\sigma)\theta\frac{\lambda}{N}\left(\frac{\gamma}{\gamma+\mu}-\frac{S_p}{N}\right)\\ 0\\ 0\end{pmatrix},\quad w^\top=\begin{pmatrix}\frac{1}{\eta_4}\\ \frac{\eta_1}{\eta_4}\\ \frac{\eta_2}{\eta_4}\\ \frac{\eta_3}{\eta_4}\\ 1\end{pmatrix}.$$

It is easy to see that $V^{-1}>0$, $w^\top>0$, and $R>0$. Thus, the first term of $\frac{d\mathcal{L}_o}{dt}$ is negative, whereas the second term is negative when $\mathcal{R}_{pt}<1$. Hence, $\frac{d\mathcal{L}_o}{dt}<0$, provided that $\mathcal{R}_{pt}<1$. The proposed function $\mathcal{L}_o$ is therefore a suitable Lyapunov function for the system (3)–(9) that can be used to establish the global stability of the DFE point.

We further note that in case where $\mathcal{R}_{pt}=1$ (which gives $\frac{d\mathcal{L}_o}{dt}=w^\top V^{-1}R$) the global stability of the DFE point can be investigated using LaSalle's invariance principle [27] by analysing the largest invariant set where $\frac{d\mathcal{L}_o}{dt}=w^\top V^{-1}R=0$. It follows that $\frac{d\mathcal{L}_o}{dt}=0$ implies $R=\mathbf{0}$. This requires $\lambda=0$ or $S=\frac{\mu N}{\gamma+\mu}$ and $S_p=\frac{\gamma N}{\gamma+\mu}$. From Eq. (14), we note that the maximum value of the total population is $\frac{\Lambda}{\mu}$, that is, $N_{\max}=\frac{\Lambda}{\mu}$. Thus, $S_{\max}=\frac{\Lambda}{\gamma+\mu}$ and $S_{pmax}=\frac{\gamma\Lambda}{\mu(\gamma+\mu)}$. On the other hand, $\lambda=0$ implies $I=I_p=I_{p^-}=T=A=0$. We therefore deduce that the largest positive invariant subset of Ω that satisfies $\frac{d\mathcal{L}_o}{dt}=0$ is the singleton $\{\mathcal{E}^0\}$. By LaSalle's invariance principle [27], the DFE point is globally asymptotically stable when $\mathcal{R}_{pt}=1$. We summarize these results in the following theorem:

Theorem 2. *The disease free equilibrium point of the model (3)–(9) is globally asymptotically stable when $\mathcal{R}_{pt}\le 1$.*

3.2.2. The endemic equilibrium point and stability analysis

In contrast to the DFE point, the endemic equilibrium corresponds to the situation in which the infection persists within the population. The endemic equilibrium point of system (3)–(9) is given by

$$\mathcal{E}^*=(S^*,S_p^*,I^*,I_p^*,I_{p^-}^*,T^*,A^*), \tag{18}$$

where

$$S^*=\frac{\Lambda}{\mathsf{E}}, \tag{19}$$

$$S_p^*=\frac{\gamma\Lambda}{\mathsf{EF}}, \tag{20}$$

$$I^*=\frac{(1-\gamma)}{(\rho_1+\mu)}\frac{\Lambda\lambda^*}{E}=a_1\frac{\Lambda\lambda^*}{\mathsf{E}}, \tag{21}$$

$$I_p^*=\frac{(1-\theta)(1-\sigma)\gamma}{(\rho_2+\mu)}\frac{\Lambda\lambda^*}{\mathsf{EF}}=a_2\frac{\Lambda\lambda^*}{\mathsf{EF}}, \tag{22}$$

$$I_{p^-}^*=\frac{\theta(1-\sigma)\gamma}{(\rho_3+\mu)}\frac{\Lambda\lambda^*}{\mathsf{EF}}=a_3\frac{\Lambda\lambda^*}{\mathsf{EF}}, \tag{23}$$

$$\begin{aligned}T^* &= \frac{\epsilon\rho_1(1-\gamma)}{(\rho_4+\mu)(\rho_1+\mu)}\frac{\Lambda\lambda^*}{\mathsf{E}}\\ &\quad+\left(\frac{\epsilon\rho_2(1-\theta)(1-\sigma)\gamma}{(\rho_4+\mu)(\rho_2+\mu)}+\frac{\epsilon\rho_2(1-\sigma)\theta\gamma}{(\rho_4+\mu)(\rho_3+\mu)}\right)\frac{\Lambda\lambda^*}{\mathsf{EF}}\\ &= a_4\frac{\Lambda\lambda^*}{\mathsf{E}}+(a_5+a_6)\frac{\Lambda\lambda^*}{\mathsf{EF}},\end{aligned} \tag{24}$$

$$\begin{aligned}A^* &= \frac{\rho_1}{g_o}\frac{g}{(\rho_1+\mu)}\frac{(1-\gamma)}{\mathsf{E}}\frac{\Lambda\lambda^*}{\mathsf{E}}\\ &\quad+\left(\frac{\rho_2}{g_o}\frac{g}{(\rho_2+\mu)}\frac{(1-\sigma)\gamma}{\mathsf{E}}+\frac{\rho_3}{g_o}\frac{g}{(\rho_3+\mu)}\frac{\theta(1-\sigma)\gamma}{\mathsf{E}}\right)\frac{\Lambda\lambda^*}{\mathsf{EF}}\\ &= a_7\frac{\Lambda\lambda^*}{\mathsf{E}}+(a_8+a_9)\frac{\Lambda\lambda^*}{\mathsf{EF}},\end{aligned} \tag{25}$$

with $\mathsf{E}=(\gamma+\mu)+(1-\gamma)\lambda^*$ and $\mathsf{F}=\mu+(1-\sigma)\lambda^*$. The coordinates of $\mathcal{E}^*$ in Eqs. (19)–(25) are determined by equating the system (3)–(9) to zero, and then solved for S^*, S_p^*, I^*, I_p^*, $I_{p^-}^*$, T^*, and A^*, respectively.

For the coordinates of $\mathcal{E}^*$ to stay in the basin of the feasible region Ω, we need $\lambda^*>0$. To guarantee this we substitute (19)–(25) into Eq. (2), which gives

$$\lambda^*=\frac{\frac{\Lambda\lambda^*}{\mathsf{EF}}(a_1\mathsf{F}+\eta_1a_2+\eta_2a_3+\eta_3(a_4\mathsf{F}+a_5+a_6)+\eta_4(a_7\mathsf{F}+a_8+a_9))}{\frac{\Lambda}{\mathsf{EF}}(\mathsf{F}+\gamma+\lambda^*(a_1\mathsf{F}+a_2+a_3+a_4\mathsf{F}+a_5+a_6+a_7\mathsf{F}+a_8+a_9))}. \tag{26}$$

Simplifying Eq. (26), we obtain the endemic polynomial

$$P(\lambda^*)=\lambda^*(C_2\lambda^{*2}+C_1\lambda^*+C_0)=0, \tag{27}$$

where

$$\begin{aligned}C_2 &= \frac{(1-\sigma)(a_1+a_2+a_7)}{\gamma+\mu},\\ C_1 &= \frac{(1-\sigma)(1-a_1-a_4\eta_3-a_7\eta_4)}{\gamma+\mu}\\ &\quad+\frac{\mu(a_1+a_4+a_7)+(a_2+a_3+a_5+a_6+a_8+a_9)}{\gamma+\mu},\\ C_0 &= 1-\mathcal{R}_{pt}.\end{aligned}$$

Eq. (27) has two non-trivial solutions: $\lambda_{1,2}^*=\frac{-C_1\mp\sqrt{C_1^2-4C_2C_0}}{2C_2}$; and one trivial solution: $\lambda_3^*=0$. The trivial solution λ_3^* corresponds to the DFE point, whilst the positive non-trivial solution $\lambda_2^*=\frac{-C_1+\sqrt{C_1^2-4C_2C_0}}{2C_2}$ corresponds to the endemic equilibrium point. It follows that $\lambda_2^*>0$, when $C_0=1-\mathcal{R}_{pt}<0$. This implies that $\mathcal{E}^*$ exists in the basin of Ω whenever $\mathcal{R}_{pt}>1$. We summarize this result as follows:

Lemma 1. *The endemic equilibrium point $\mathcal{E}^*$ of the model (3)–(9) exists only when $\mathcal{R}_{pt}>1$.*

Next, we claim the following:

Theorem 3. *The endemic equilibrium point of the model (3)–(9) is globally asymptotically stable when $\mathcal{R}_{pt}>1$.*

Proof. To investigate the global stability of the endemic equilibrium point $\mathcal{E}^*$, we define a function $\mathcal{L}_e$ given by

$$\mathcal{L}_e=\sum_{i=1}^{7}\mathtt{D}_i\mathcal{L}_i,\quad \mathtt{D}_i>0, \tag{28}$$

where

$$\mathcal{L}_i=x_i-x_i^*-x_i^*\ln\frac{x_i}{x_i^*},\ \text{for } x_i\in\mathcal{V}=\{S,S_p,I,I_p,I_{p^-},T,A\}.$$

Clearly, each function $\mathcal{L}_i$, $i=1,\dots,7$, is positive definite, continuous and differentiable in Ω. Hence, $\mathcal{L}_e\in\mathcal{C}^1[\Omega,\mathbb{R}^+]$. Moreover,

equating the first partial derivatives of $\mathcal{L}_e$ with respect to each x_i to zero, i.e

$$\frac{\partial \mathcal{L}_e}{\partial x_i} = \mathtt{D_i}\left(1 - \frac{x_i^*}{x_i}\right) = 0,$$

yields $x_i = x_i^*$, which means $S_p = S_p^*$, $I = I^*$, $I_p = I_p^*$, $I_{p^-} = I_{p^-}^*$, $T = T^*$, and $A = A^*$. It therefore follows that the endemic equilibrium point is the only stationary point of the function $\mathcal{L}_e$.

In addition, the second partial derivatives of $\mathcal{L}_e$ with respect to each x_i, given by

$$\frac{\partial^2 \mathcal{L}_e}{\partial x_i^2} = \mathtt{D_i}\frac{x_i^*}{x_i^2},\ i = 1, \ldots, 7 \tag{29}$$

are all positive. Hence, the endemic equilibrium is a global minimum point of the function $\mathcal{L}_e$, for all $x_i \in \Omega \subseteq \mathbb{R}_+^7$.

Now we need to show that $\mathcal{L}_e$ is a Lyapunov function. For that, it suffices to show that the time derivative $\frac{d\mathcal{L}_e}{dt}$ of $\mathcal{L}_e$,

$$\frac{d\mathcal{L}_e}{dt} = \sum_{i=i}^{7} \mathtt{D_i}\frac{dx_i}{dt} - \sum_{i=i}^{7} \mathtt{D_i}\frac{x_i^*}{x_i}\frac{dx_i}{dt}, \tag{30}$$

is negative definite for all $t > 0$. We know that for all $x_i \in \Omega$, $\frac{dx_i}{dt} \leq \dot{N}$. Thus Eq. (30) becomes

$$\frac{d\mathcal{L}_e}{dt} \leq \sum_{i=i}^{7} \mathtt{D_i}\left(1 - \frac{x_i^*}{x_i}\right)\dot{N}. \tag{31}$$

Differentiating both sides of (13), we have $\dot{N} \leq \mu\left(\frac{\Lambda}{\mu} - N(0)\right)e^{-\mu t}$. Eq. (31) becomes

$$\frac{d\mathcal{L}_e}{dt} \leq \sum_{i=i}^{7} \mathtt{D_i}\left(1 - \frac{x_i^*}{x_i}\right)\mu\left(\frac{\Lambda}{\mu} - N(0)\right)e^{-\mu t}. \tag{32}$$

We note from Eq. (32) that when the total initial population $N(0)$ stays in the basin of Ω, i.e $N(0) \leq \frac{\Lambda}{\mu}$, $\frac{d\mathcal{L}_e}{dt} \leq 0$, as $t \to \infty$. Otherwise, if $N(0) > \frac{\Lambda}{\mu}$, the right-hand side of Eq. (31) is negative definite, therefore $\frac{d\mathcal{L}_e}{dt} \leq 0$. Therefore, regardless of the initial population size $N(0)$, $\frac{d\mathcal{L}_e}{dt} \leq 0$, for all time $t > 0$. Thus, the proposed function $\mathcal{L}_e$ is a Lyapunov function. $\mathcal{L}_e$ can be used to prove the global stability of the endemic equilibrium point. In addition, we note that $\frac{d\mathcal{L}_e}{dt} = 0$ if and only if $x_i = x_i^*$, i.e $S = S^*$, $S_p = S_p^*$, $I = I^*$, $I_p = I_p^*$, $I_{p^-} = I_{p^-}^*$, $T = T^*$, and $A = A^*$. The largest positive invariant subset of Ω that satisfies $\frac{d\mathcal{L}_e}{dt} = 0$ is the singleton $\{\mathcal{E}^*\}$.

In summary, we note that when $\mathcal{R}_{pt} > 1$, the system has a unique endemic equilibrium point $\mathcal{E}^*$ in the interior of Ω, which is globally asymptotically stable. This completes the proof. □

The analysis of the stability conditions of both equilibrium points (indicated in Theorems 2 and 3) are to investigate the resulting state of the infection within the population once one (or more than one) of the state variables $x_i \in \Omega$ is subjected to a small variation (ε_i), i.e $x_i \longrightarrow x_i \pm \varepsilon_i$. Such a perturbation may possibly shift the corresponding state variable away from its steady state value. The local stability tells us that the infection process will return back to the steady state on its own if the modified state value is near the starting steady state. The global stability shows that the infection process can reverse to the steady state (with time) regardless of the modified state value. From the results obtained, we deduce that, unless perturbed, the steady state value of the state variables would remain unchanged over time, provided that the indicated conditions ($\mathcal{R}_{pt} > 1$ or $\mathcal{R}_{pt} \leq 1$) hold. The model undergoes a supercritical bifurcation as shown in Fig. 2.

3.3. Analysis of the control reproduction number

In this section, we investigate the benefit of coupling PrEP intervention with ARV treatment. We also analyse the impact of the PrEP resistance rate, θ, on the HIV infection spread using the control reproduction number $\mathcal{R}_{pt}$.

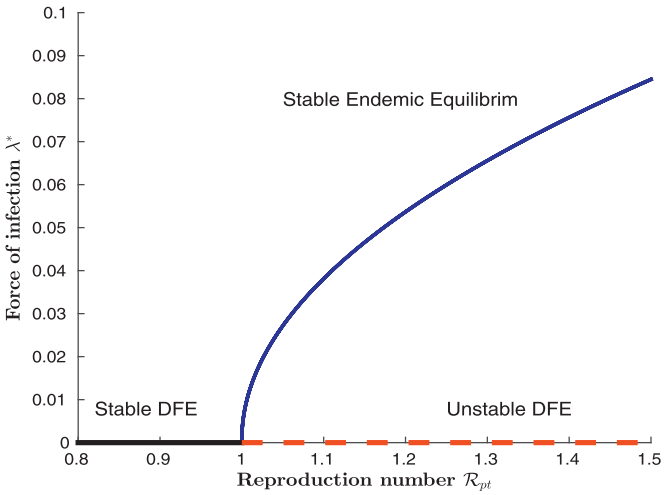


Fig. 2. Bifurcation diagram showing a forward bifurcation of λ^* versus $\mathcal{R}_{pt}$ with parameter values from Table 2.

Let $\mathcal{R}_p$ be the control reproduction number of the model when PrEP is effectively implemented as the only control measure. In this case, the system (3)–(9) is reduced to six compartments and the corresponding control reproduction number $\mathcal{R}_p$ is given by

$$\mathcal{R}_p = \frac{g_{p1}(\delta + \mu + \eta_4\rho_1)}{(\rho_1 + \mu)(\delta + \mu)} + \frac{g_{p2}(\eta_1(\delta + \mu) + \eta_4\rho_2)}{(\rho_2 + \mu)(\delta + \mu)} + \frac{g_{p3}(\eta_2(\delta + \mu) + \eta_4\rho_3)}{(\rho_3 + \mu)(\delta + \mu)}, \tag{33}$$

where $g_{p1} = \frac{c(1-\gamma)\mu}{\gamma+\mu}$, $g_{p2} = \frac{c(1-\theta)(1-\sigma)\gamma}{\gamma+\mu}$, $g_{p3} = \frac{c\theta(1-\sigma)\gamma}{\gamma+\mu}$.

For the situation where no pre-infected individuals on PrEP are detected, i.e $\theta = 0$, $\mathcal{R}_p$ becomes

$$\mathcal{R}_{po} = \frac{c(1-\gamma)\mu(\delta + \mu + \eta_4\rho_1)}{(\gamma + \mu)(\rho_1 + \mu)(\delta + \mu)} + \frac{c(1-\sigma)\gamma(\eta_1(\delta + \mu) + \eta_4\rho_2)}{(\gamma + \mu)(\rho_2 + \mu)(\delta + \mu)}. \tag{34}$$

To assess the impact of θ on $\mathcal{R}_p$, we compute $\Delta_p^{po} = \mathcal{R}_p - \mathcal{R}_{po}$, which gives

$$\Delta_p^{po} = \frac{g_{p3}\mu(\eta_2 - \eta_1)}{(\rho_2 + \mu)(\rho_3 + \mu)} + \frac{g_{p3}\mu\eta_4(\rho_3 - \rho_2)}{(\rho_2 + \mu)(\rho_3 + \mu)(\delta + \mu)} + \frac{g_{p3}(\rho_2\eta_2 - \rho_3\eta_1)}{(\rho_2 + \mu)(\rho_3 + \mu)(\delta + \mu)}. \tag{35}$$

The first two terms of Eq. (35) are positive since we assumed (in Section 2) that $\eta_2 > \eta_1$ and $\rho_3 > \rho_2$. Hence, Δ_p^{po} is positive, i.e $\mathcal{R}_{po} < \mathcal{R}_p$, if and only if the last term of Eq. (35) is positive, i.e when $\frac{\eta_1}{\rho_2} < \frac{\eta_2}{\rho_3}$. Parameter η_1 (respectively η_2) represents the transmissible rate of infected individual in I_p (respectively I_{p^-}), whereas $\frac{1}{\rho_2}$ (respectively $\frac{1}{\rho_3}$) represents the average period of time spent in the $I_p(t)$ (respectively $I_{p^-}(t)$) class. The term $\frac{\eta_1}{\rho_2}$ (respectively $\frac{\eta_2}{\rho_3}$) is the probability that a susceptible individual is infected by an individual I_p (respectively I_{p^-}) during his/her infectious period in the $I_p(t)$ (respectively $I_{p^-}(t)$) class. This result indicates that PrEP drug resistance influence on the spread of HIV infection would depend on the transmissibility rate and the duration of inadvertent PrEP use by already-infected individuals.

We also investigate conditions under which it is more beneficial to undertake PrEP intervention in conjunction with ARV treatment

than PrEP intervention alone. We compute $\Delta^p_{pt} = \mathcal{R}_{pt} - \mathcal{R}_p$ to obtain

$$\Delta^p_{pt} = \left(\frac{g_1\epsilon\rho_1}{\rho_1+\mu} + \frac{g_2\epsilon\rho_2}{\rho_2+\mu} + \frac{g_3\epsilon\rho_3}{\rho_3+\mu}\right)\left(\eta_3 - \frac{\eta_4\mu}{\delta+\mu}\right).$$

PrEP and ARV treatment interventions (both concurrently implemented) will be a more effective intervention in combating HIV infection spread than PrEP intervention alone if $\Delta^p_{pt} < 0$, i.e $\eta_3 - \frac{\eta_4\mu}{\delta+\mu} < 0$. The inequality implies that $\frac{\eta_3}{\eta_4} < \frac{\mu}{\delta+\mu} < 1$, which gives $\eta_3 < \eta_4$, a condition consistent with the prior assumption made in the model formulation. This result simply suggests that PrEP intervention and ARV use, when implemented concurrently, will meaningfully contribute to curtailing the spread of HIV infection. The constraints $\frac{\eta_1}{\eta_2} < \frac{\rho_2}{\rho_3} < 1$ and $\frac{\eta_3}{\eta_4} < \frac{\mu}{\delta+\mu} < 1$ predict the challenges which might be encountered in a long lasting-control of HIV infection with both interventions.

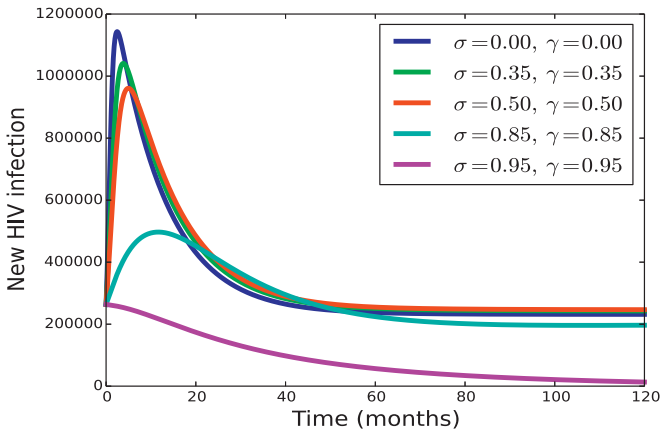
4. Numerical simulations

Numerical simulations of the model are performed to support the analytical results and also to obtain a broad view of the time evolution of the infected populations. The model simulation results shall help in validating the potential benefits of PrEP and ARV therapy when used concurrently or separately in controlling HIV infection progression. The contribution of the PrEP resistance rate into HIV infection spread will be investigated as well.

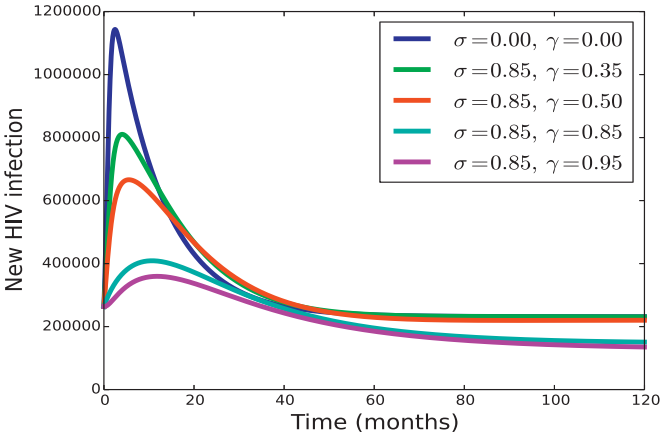
We use the recent WHO and Botswana fourth HIV/AIDS impact survey of 2013 [28] for the initial conditions of our model system. We target Botswana for our model validation due to the small size of the population and their effective handling and implementation of HIV health care programs. In 2002, Botswana was one of the few sub-Saharan countries capable of providing free ARV therapy to all infected individuals seeking treatment. HIV test scopes and ARV treatment coverage in Botswana are quite high compared to other African countries. From report [28], 63.7% of the population aged 15–49 years have had an HIV test and were informed of their HIV status. At the end of 2014, there were 34 ART sites and 561 satellite clinics across the country dispensing ARVs. The national ARV census data indicated that there were 247,947 children and adults on highly active anti-retroviral therapy (HAART), which translates to 63.2% of the total people living with HIV (which is lower than 69.9% recorded in 2013) [29]. We therefore see Botswana as a good and suitable example for effective PrEP implementation alongside their existing treatment program. In 2013, the Botswana population was estimated at 2,045,752, within which 1,085,001 adults are aged between 15 and 49 years old, of whom 24% are living with HIV infection [28]. For our model simulations, we assume the initial density of the model sub-populations to be

$$S(0) = 1,085,001, \quad S_p(0) = 0, \quad I(0) = 263,655,$$
$$I_p(0) = I_{p^-}(0) = T(0) = A(0) = 0.$$

According to the latest WHO data [30], life expectancy in Botswana is 63.0 years for males and 65.4 years for females, with a total life expectancy of 64.2 years, which gives Botswana a world life expectancy ranking of 144th. The natural death rate is defined as the reciprocal of the life expectancy. Hence, $\mu = 0.015$ per year. It was also reported that in 2014, HIV/AIDS deaths in Botswana reached 5,624, that is 37,61% of total deaths, ranking Botswana 6th in the world. This gives $\delta = 0.376$. The current HIV incidence for Botswana is documented to be 1.35% [29]. From this same report, approximately sixteen percent (15.8%) of women and men aged 15–49 years have had sexual intercourse with more than one partner during the 12 months of 2013. This indicates that the average number of new sexually active partners acquired per year is greater than one. The other parameter values used in our model



(a)



(b)

Fig. 3. Simulations of new HIV infections $(I(t) + I_p(t) + I_{p^-}(t))$ for various levels of PrEP efficacy and PrEP awareness with constant ART rate ($\epsilon = 0.63$). Parameter values are taken from Table 2 with (a) (σ, γ) varying from 0 to 95%, and (b) $0 \le \gamma \le 0.95$ but with σ fixed at 0.85.

are indicated and referenced in Table 2. With these data, we consider various possible PrEP interventions with distinct proportions of sexually active individuals enrolled in PrEP programs with distinct PrEP efficacy levels delivered. Unlike other studies, we will not distinguish between Tenofovir-based or Truvada-based PrEP interventions. We will characterise high PrEP awareness when the proportion of the susceptible individuals (γ) enrolled in PrEP use ranges between 90% and 100%, otherwise PrEP awareness will be classified as low ($\gamma < 50\%$) or moderate ($50 \le \gamma \le 89\%$). We vary ARV treatment rates from 0% to 63.2% with reference to the report [29]. The PrEP resistance rates range from 0 to 7.9% [31]. The simulation results are presented in Figs. 3, 4 and 5.

Fig. 3(a) shows the time evolution of the total new HIV infections with different PrEP interventions while ARV treatment is held at a constant rate $\epsilon = 63\%$. We observe a significant decrease in the peak values of the total new HIV infected individuals when PrEP awareness and PrEP efficacy gradually increase. This result emphasizes the potential benefits of PrEP intervention when implemented at higher levels. We also note that the highest peak value is reached when PrEP is not applied (i.e only ARV treatment is applied). This confirms the necessity of introducing PrEP use in high risk communities to address the limitations of ARV interven-

Table 2
Table of parameter values and their description.

Parameter	Description	Value (/yr)	Source
Λ	Recruitment rate	20,840	Assumed
γ	PrEP awareness level	[0, 0.99]	[32]
σ	PrEP efficacy level	[0, 0.99]	[14]
ϵ	Rate of being put on treatment	[0, 0.632]	[29]
θ	PrEP resistance rate	[0, 0.079]	[31]
μ	Natural death rate	0.015	[30]
δ	AIDS related death rate	0.376	[30]
ρ_1	Progression rate out of $I(t)$ class	0.074	[33]
ρ_2	Progression rate out of $I_p(t)$ class	0.060	Assumed
ρ_3	Progression rate out of $I_{p^-}(t)$ class	0.080	Assumed
ρ_4	Progression rate from $T(t)$ to $A(t)$ class	0.052	Assumed
η_1	Transmission rate per act in $I_p(t)$ class	0.0219	[14]
η_2	Transmission rate per act in $I_{p^-}(t)$ class	1.215	Assumed
η_3	Transmission rate per act in $T(t)$ class	0.0135	[29]
η_4	Transmission rate per act with $A(t)$ individual	1.250	Assumed
c	Average number of unsafe sexual acts	2	[29]

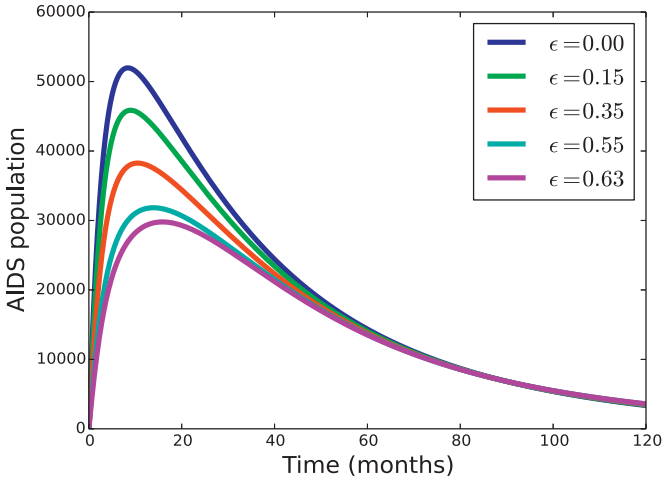
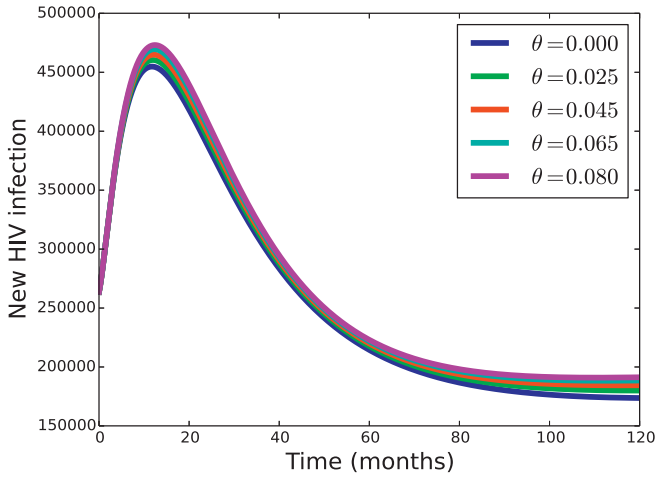


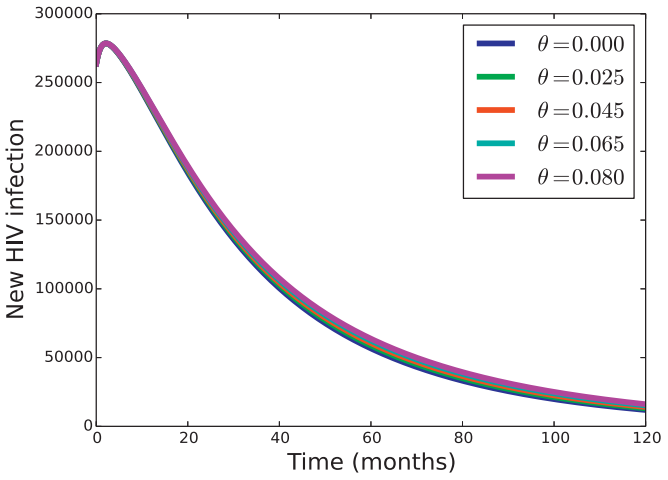
Fig. 4. Simulations of time variations of the AIDS population, $A(t)$, for various ARV treatment rates while maintaining a constant PrEP level ($\sigma = 0.95$, $\gamma = 0.95$), and PrEP drug resistance ($\theta = 0.079$), with other parameter values taken from Table 2.

tion in reducing new HIV infections. In comparing the peak values for the case when PrEP is not applied (the blue curve), with the case when PrEP and ARVs are applied (the green curve), we record 150,000 new HIV infections averted in the first half year, a reduction of 13%. In addition, our model predicts that when PrEP is implemented (alongside the ARV treatment) at a high level (>92%), new infections will immediately decrease from the initial implementation time and continuously tend to zero. No peak value is observed for that scenario. Our model prediction is thus in agreement with the characterisation of PrEP effectiveness beyond 92% as a high PrEP level in previous studies.

To stratify the impact of PrEP efficacy from PrEP awareness in Fig. 3(a), we hold all the parameter values unchanged but lower the efficacy level from 95% to 85%. The result is presented in Fig. 3(b) which shows that with low PrEP efficacy, a decrease of the new infected individuals is probable but over a long time, compared to the case when high PrEP efficacy is taken into account. This calls for PrEP efficacy pharmacovigilance. In Fig. 4, we vary the ARV treatment rate while maintaining a constant PrEP level ($\sigma = 0.95$, $\gamma = 0.95$). We do this to illustrate the total number of AIDS individuals over time. The model predicts that the number of individuals developing full blown AIDS will decrease with an increase of the treatment rate. We note that the highest peak is reached when no treatment program is administered (i.e only PrEP intervention). This result indicates that PrEP intervention alone might not fully help in mitigating the endemicity level



(a)



(b)

Fig. 5. Simulations of new HIV infections ($I(t) + I_p(t) + I_{p^-}(t)$) for distinct PrEP drug resistance rates, $0 \leq \theta \leq 0.080$, with PrEP levels and ART rate held constant. Parameter values are taken from Table 2 with (a) $\sigma = 0.85$, $\gamma = 0.90$, $\epsilon = 0.63$, and (b) $\sigma = 0.95$, $\gamma = 0.90$, $\epsilon = 0.63$.

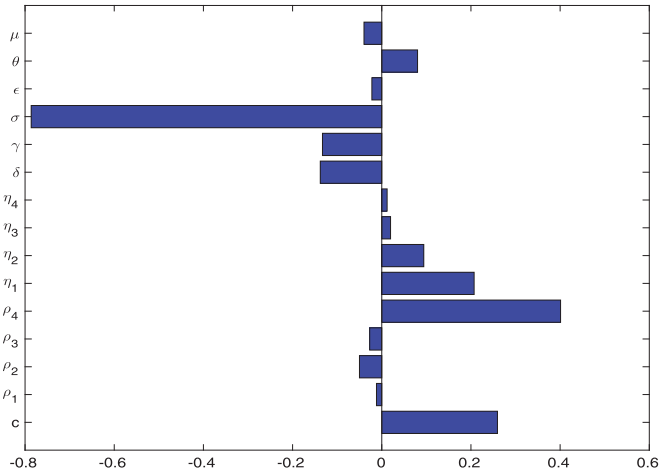


Fig. 6. Partial rank correlation coefficients showing the effect of parameter variation on $\mathcal{R}_{pt}$. Parameters with positive PRCCs will increase the value of $\mathcal{R}_{pt}$ when their value is increased, whereas parameters with negative PRCCs will decrease $\mathcal{R}_{pt}$, when their value is increased.

of HIV infection. In other words, our results underscore the importance of coupling PrEP intervention and ARV therapy in the fight against the HIV pandemic.

In Figs. 5(a) and (b), we show the impact of PrEP resistance on the cumulative new HIV infections by increasing the value of θ from 0 to 0.080. The simulation result presented in Fig. 5(a) shows a significant contribution of the PrEP resistance rate into the spread of HIV infection, while PrEP efficacy, PrEP awareness and ARV treatment rates are taken at 85%, 90%, and 63%, respectively. However, we observe from Fig. 5(b) that when PrEP efficacy is at a high level ($\sigma = 0.95$), the increase of new HIV infections is quite minimal. This simply illustrates that in order to mitigate the contribution of PrEP resistance to HIV infection spread PrEP efficacy needs to be maintained at a high level.

4.1. Sensitivity analysis

We performed sensitivity analysis on $\mathcal{R}_{pt}$ using Partial Rank Correlation Coefficients (PRCCs) with a thousand simulations per run to investigate the most influential parameters on $\mathcal{R}_{pt}$. The results are presented in Fig. 6. PrEP efficacy is shown to be the most sensitive factor in reducing the value of $\mathcal{R}_{pt}$, while the progression rate of infected individuals on treatment to the AIDS stage and the average number of risky transmissions per sexual acts are the most influential factors in the increase of $\mathcal{R}_{pt}$.

We also conducted PRCCs and Monte Carlo simulations to explore the impact of the variation of parameter values on the already-infected PrEP user population. The results are presented in Fig. 7. Parameters with positive PRCCs will increase $I_{p^-}(t)$ when their value is increased, whereas parameters with negative PRCCs will decrease $I_{p^-}(t)$, when their value is increased. These results support the earlier findings in Fig. 5(a) and (b), that an increase in PrEP efficacy level has a potent impact in reducing the contribution of the already-infected individuals to the HIV infection spread.

5. Discussion

In this study, a mathematical model describing HIV infection dynamics in an homogeneously mixing population was developed to assess the benefit of coupling ARV use for treatment and PrEP use for prevention, with drug resistance, in the fight against HIV infection progression. The model fundamental properties, such as the biological feasible region, the epidemic threshold ($\mathcal{R}_{pt}$), the equilibrium points, and the stability thereof, were rigorously analysed. The analyses indicated that the model has two equilibrium

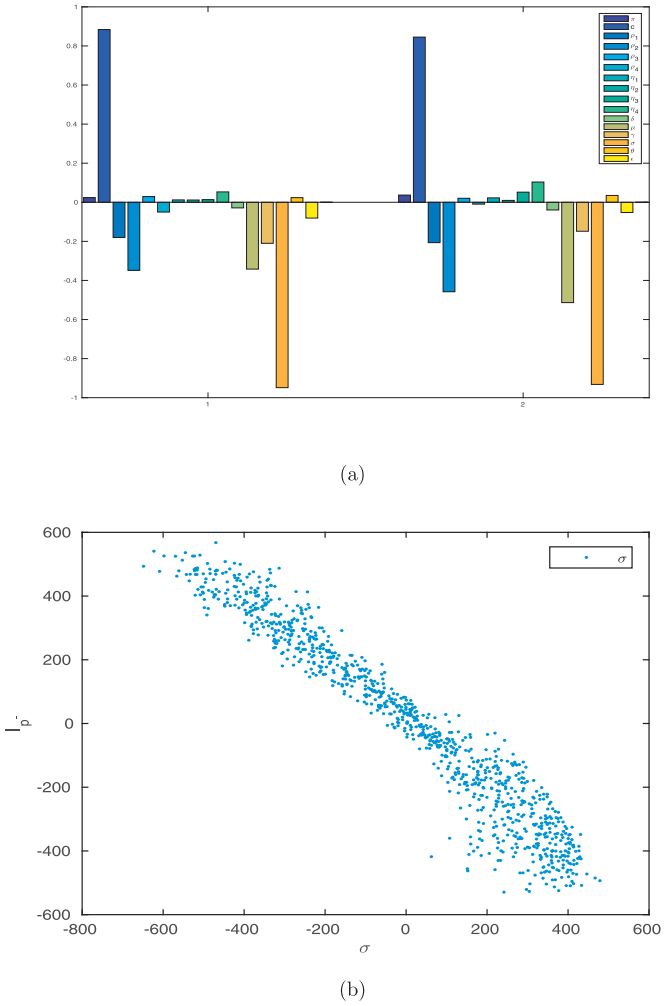


Fig. 7. (a) Partial rank correlation coefficients and (b) Monte Carlo simulations of one thousand sample values for $I_{p^-}(t)$ sub-population versus the PrEP efficacy (σ), with parameter values given in Table 2. Parameters with positive PRCCs will increase the density of $I_{p^-}(t)$ when their value is increased, whereas parameters with negative PRCCs will decrease $I_{p^-}(t)$, when their value is increased.

points, the disease free equilibrium (DFE) point and the endemic equilibrium point. The DFE point was shown to be globally asymptotically stable when $\mathcal{R}_{pt} \leq 1$, whereas the endemic equilibrium exists and is globally asymptotically stable when $\mathcal{R}_{pt} > 1$. The model analysis showed that implementation of both strategies in communities where high risk of HIV infection prevails reduced HIV incidence more significantly than when either strategy is implemented as a single intervention. Furthermore, numerical simulations of the model confirmed that combined PrEP and ARV intervention offers the best potential for substantial new HIV infection reduction. In addition, the simulations revealed that for both interventions, high adherence is key to effectiveness. The PrEP efficacy level was found to be important for effective reduction of new HIV infections. The model thus alerts us to PrEP pharmacovigilance if PrEP implementation along with ARV therapy is to be effective. Inadvertent PrEP use by already-infected individuals, which generates PrEP drug resistance, was also part of our model analysis. The model results showed that an increase in the number of misdiagnosed infected individuals on PrEP could be a key driver of HIV infection spread, and is hence a crucial hurdle to curtail HIV infection spread by PrEP and ARV use interventions.

Our model can be modified to include other important factors influencing the spread of HIV infections. In particular, we can refine the epidemiological assumptions made in order to improve

the precision of the model outcomes. Appropriate data on PrEP and ARV use including PrEP resistance data can be used to improve model and its outcomes. Discontinuation of PrEP use (resulting from side effects, financial means, unavailability of the drugs) can also be incorporated. HIV incidence per gender, cost effectiveness, cost benefit analysis and optimal control theory to investigate whether PrEP use for HIV control should be time independent (supply at a constant value) or time dependent (supply according to the demand of the time) are also some of the factors that can be included for better predictions.

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Chapter 4

Optimizing PrEP and post-HIV infection control strategies

Optimizing PrEP and post-HIV infection control strategies

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Abstract

We present a mathematical model describing HIV infection dynamics in an homogeneous population where pre-exposure prophylaxis (PrEP) drugs are accessible and post-HIV infection support services are scheduled. The model is used to investigate the benefits of PrEP use as potential HIV infection prevention intervention and post-infection support services. Thus, PrEP awareness, PrEP efficacy, and post-infection HIV education are some of the key control factors considered throughout the analysis of the model. The controls are considered time independent while analysing the endemicity conditions of the infection, and then time dependent to investigate the optimal efforts and necessary costs needed to mitigate the infection endemicity level and possible total eradication. The analytical and numerical results obtained suggest best practice for effective HIV infection eradication through a successful PrEP program implementation.

Keywords: PrEP efficacy, PrEP awareness, HIV status, optimal control.

1. Introduction

The major transmission routes for HIV infection are: (1) horizontal transmission (during unsafe sexual contact), (2) vertical transmission (infected pregnant mother to child or during breast feeding), and (3) direct injection with contaminated tools (needles, syringes, knife) during blood transfusion. Transmission through sexual contact remains the most common transmission mode. This has underscored the importance of intensifying prevention efforts to reduce transmission related to unsafe sexual contact. The "ABC" strategies (Abstinence, Be faithful to HIV-partner, Condom use), reduction of the number of sexual partners, sterilisation of all blood tools, and male circumcision are some of the first intervention strategies against the HIV infection. However, their implementation has been largely affected by factors such as culture, financial income, gender inequalities, and inadequate facilities. These behavioural interventions have thus not universally been able to contain the pandemic. There is a need to have more effective preventive strategies to contain HIV infection progression. More than 20 antiretroviral drugs (ARVs) are currently available. These drugs, when used properly,

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have a potential to suppress the viral load of the infected patient. This allows the immune system response to recover and improve its effectiveness against the virus and subsequently extends one's lifespan. The ARVs have managed to avert early AIDS related deaths and significantly reduced the likelihood of HIV infection transmission. For instance, in serodiscordant couples the risk of infecting the HIV-negative partner is reduced by between 63% and 73% when the HIV-positive partner is taking ARVs [1]. In addition, an HIV-positive pregnant mother on consistent antiretroviral therapy would reduce perinatal transmission. Zidovudine (ZDV) used before, during, and after delivery reduced vertical transmission rate from 25.5% to 8.3% [2]. Perinatal HIV transmission prevention has been the most successful HIV prevention strategy to date. ARVs are also recommended to be taken within 72 hours when one is exposed to the virus [3]. ARVs have been a reliable means for the treatment of people living with HIV infection and a potential measure to reduce HIV infection rate. Between 1996 and 2012, ARVs treatment averted 6.6 million AIDS related deaths worldwide, including 5.5 million deaths in low-and middle-income countries [4].

All the aforementioned findings have boosted the hope of possible HIV vaccine finding and stimulated the concept of prescribing antiretroviral drugs to susceptible individuals in the form of pre-exposure prophylaxis (PrEP). PrEP is simply a preventive medicine or preventive care consisting of measures taken to prevent the outbreak of some diseases rather than curing them or treating their symptoms. PrEP should be distinguished from post-exposure prophylaxis (PEP), in which an individual takes ARVs soon after a potential HIV exposure with the goal of reducing the likelihood of infection [5]. PrEP has been successfully practised for other disease prevention such as malaria, influenza, and even for birth control. In case of HIV, PrEP is administrated as a daily oral pill or microbicide gel by susceptible individuals at a high-risk of infection. PrEP is a novel approach to HIV prevention that is systematically directed to people at high risk such as commercial sex workers, injecting drugs users, or people for whom consistent condom use have proven difficult.

In exploring PrEP effectiveness, a large number of clinical trials and studies of HIV PrEP intervention have been undertaken and works still ongoing in different countries including Peru, Thailand, Botswana, United States, and Nigeria, etc. Two PrEP drugs (Tenofovir Fumarate/TDF and Truvada/TDF+emtricitabine) were approved by the United States Food and Drugs Administration (FDA) for their use in high risk groups as a form of PrEP. A dose of 300 mg TDF alone or in combination with 200/245mg of emtricitabine (yielding Truavada) was shown to significantly reduce the risk of sexually acquisition of HIV infection in men and women. The PrEP drug use for HIV infection prevention is an additional and promising preventive mode of HIV infection. A healthy individual keen to be on PrEP use for HIV infection prevention is recommended to be tested first in order to ensure that he/she is HIV negative. Many individuals are currently ignorant of their HIV status. Thus, PrEP program when effectively implemented can play an important role in ongoing efforts for comprehensive HIV prevention and maximum HIV screening programs as well as proper post-infection monitoring [6].

Results from some theoretical studies analysing the risk perception of PrEP use and PrEP effectiveness have brought attention to the level of PrEP adherence as well as PrEP efficacy level [7, 8, 9, 10]. Rahman *et al.* [11] developed a HIV/AIDS model investigating the impact of Tenofovir gel as PrEP on HIV infection. Their simulation results, fitted with data from South Africa, suggested that the effective reduction of HIV infection through sexual intercourse depends highly on its adherence and coverage. Conway *et al.* [3] worked on stochastic models based on continuous-time branching process to analyse the pre- and post-exposure prophylaxis interventions against HIV infection considering different scenarios. A study by Vissers *et al.* [12] used a mathematical model to fit data collected from some countries which rolled out PrEP use in different variable such as gender, level of risk, stage of infection and PrEP adherence is presented. The results obtained from the analysis suggested that high risk behaviour reduced the impact of PrEP use. In [13], Mushayabasa highlighted the effects of the role played by the HIV/AIDS support groups, HIV test and post HIV infection counsellings in combating new HIV infections. The studies in [14] shed light on the impact of HIV screening of unaware infectives for optimal control and treatment of HIV/AIDS. Inspired by these previous studies on HIV infection and the PrEP drug use for HIV infection prevention, we intend in this study to examine and shed light on the impact of PrEP awareness, PrEP efficacy level, HIV screening and post-infection education required to alleviate the HIV infection incidence in community using optimal control theory. We strongly believe that understanding the mathematical behaviour and the effects in change of the value of these control factors in HIV infection dynamics is very important.

We organise this article as follows: in section 2, we elucidate the essential dynamics of the HIV infection within a population where a PrEP program and post-infection educational service are scheduled, which led to a system of ordinary differential equations (ODEs) that mathematically model the infection dynamics. In section 3, qualitative analysis of the model important features is carried out. In section 4, stability conditions of the model equilibrium points are investigated. In Section 5, optimal control theory is incorporated into the analysis, using Pointryagin's maximum principle. In section 6, numerical simulations are presented with discussion thereof.

2. Model Formulation

We consider a community with a total population of $N(t)$ individuals at risk of HIV infection at any time t, and where HIV PrEP drugs, voluntary HIV screening, and post-infection education services are accessible. On the basis of their HIV status and the health decision taken, the $N(t)$ individuals are subdivided, at time $t > 0$, into seven distinct subclasses, namely: susceptible non-PrEP users who do not know their HIV status $S(t)$, susceptible PrEP users who know their status and decide to enrol into PrEP drugs administration $S_p(t)$, infected non-PrEP users who do not know their HIV status $I_d(t)$, infected PrEP users who do not know that PrEP has failed to protect them $I_{dp}(t)$, infected individuals who know their HIV status and who still indulge in risky sexual activities $I_{kr}(t)$, infected individuals who know their HIV status and who

have withdrawn from risky sexual behaviour $I_{kn}(t)$, and AIDS individuals $A(t)$. We assume that the AIDS individuals are weak and symptomatic, and therefore considered sexually inactive. As a result, they do not influence the spread of HIV. In addition, the population is assumed to be uniform and homogeneously mixed so that the total population is given by

$$N(t) = S(t) + S_p(t) + I_d(t) + I_{dp}(t) + I_{kr}(t) + I_{kn}(t) + A(t). \tag{1}$$

HIV transmission dynamics in this population is assumed to be through horizontal transmission, so only sexually active individuals shall be considered in this study. A successful HIV infection transmission resulting from sexual contact between a susceptible individual and an infected individual from $I_d(t)$, $I_{dp}(t)$, and $I_{kr}(t)$ classes are assumed to be at the rates η_1, η_2 and η_3, so that $\eta_2 < \eta_3 < \eta_1$, respectively, and the force of infection λ is given by

$$\lambda = \frac{c\eta_1 I_d(t) + c\eta_2 I_{dp}(t) + c\eta_3 I_{kr}(t)}{N(t)}, \tag{2}$$

where the parameter c represents the average number of new sexually active partners that each infected individual acquires per unit time. We assume that individuals in $I_d(t)$ and $I_{dp}(t)$ classes are screened for HIV infection at the rate w_1 and w_2, respectively, so that $w_1 < w_2$. This inequality spans from the fact that in factual PrEP regimen, PrEP users are more regularly tested than the non-PrEP users. The proportion of the susceptible individuals on PrEP drug use is assumed to be γ, $0 < \gamma \leq 1$, where γ hypothetically measures the PrEP awareness level. The remaining proportion $(1 - \gamma)S$ not on PrEP may engage in risky sexual behaviour and become infected at rate $(1 - \gamma)\lambda$. In addition, we assume that among the susceptible individuals who seek PrEP protection with consistent adherence to prescription, only a proportion σ get protected (σ thus measures the PrEP drugs efficacy level), and $(1 - \sigma)S_p$ individuals are exposed to HIV infection risk and become infected at the rate $(1-\sigma)\lambda$. Factors such as waning, side-effects, and financial problems may affect the adherence. Thus, PrEP users interrupt the intake of the medication and hence move back to the susceptible class at rate α, where $0 \leq \alpha \leq 1$, before they become infected. We also assume that once aware of their HIV status, infected individuals are encouraged to enrol in HIV-positive support service programs where comprehensive post-infection healthcare education is dispensed. As a result, we assume that a certain proportion of HIV-positive individuals decide to reduce their risky sexual activities whilst the remaining proportion does not. We thus assume a fraction ϱ_1 (respectively ϱ_2) of the $w_1 I_d(t)$ individuals (respectively $w_2 I_{dp}(t)$) tested HIV-positive and who have received the post-infection education, are practising safe sex so that they are moved to the $I_{kn}(t)$ class, whilst the remaining $(1 - \varrho_1)w_1 I_d(t)$ individuals (respectively $(1 - \varrho_2)w_2 I_{dp}(t)$) are assumed to continue engaging in risky sexual activities, and thus move to the $I_{kr}(t)$ class. Infected individuals in the $I_{kn}(t)$ class who have withdrawn from risky sexual activities may relapse into risky behaviour at rate θ_w; and conversely, individuals in $I_{kr}(t)$ may change their sexual behaviour at a rate θ_a. The progression rates from infected classes $I_d(t)$, $I_{dp}(t)$, $I_{kr}(t)$, and $I_{kn}(t)$ to the AIDS class $A(t)$ are taken to be

ρ_1, ρ_2, ρ_3, and ρ_4, respectively, so that $\rho_4 < \rho_2 < \rho_3 < \rho_1$. The natural death rate and death related to the disease rate are assumed to be μ and δ, respectively. Individuals are then recruited into the susceptible non-PrEP users class $S(t)$, at a constant rate π. A pictorial illustration of the flow of individuals in the seven classes is presented in Figure 1 and mathematically modelled as follows:

$$\begin{aligned}
\dot{S} &= \pi - \gamma S - (1-\gamma)\lambda S + \alpha S_p - \mu S, && (3)\\
\dot{S}_p &= \gamma S - (1-\sigma)\lambda S_p - (\alpha+\mu) S_p, && (4)\\
\dot{I}_d &= (1-\gamma)\lambda S - w_1 I_d - (\rho_1+\mu) I_d, && (5)\\
\dot{I}_{dp} &= (1-\sigma)\lambda S_p - w_2 I_{dp} - (\rho_2+\mu) I_{dp}, && (6)\\
\dot{I}_{kr} &= (1-\varrho_1) w_1 I_d + (1-\varrho_2) w_2 I_{dp} + \theta_w I_{kn} - (\theta_a + \rho_3 + \mu) I_{kr}, && (7)\\
\dot{I}_{kn} &= \varrho_1 w_1 I_d + \varrho_2 w_2 I_{dp} + \theta_a I_{kr} - (\theta_w + \rho_4 + \mu) I_{kn}, && (8)\\
\dot{A} &= \rho_1 I_d + \rho_2 I_{dp} + \rho_3 I_{kr} + \rho_4 I_{kn} - (\mu+\delta) A, && (9)
\end{aligned}$$

with non-negative initial conditions $S(0) = S_0$, $S_p(0) = S_{p0}$, $I_d(0) = I_{d0}$, $I_{dp}(0) = I_{dp0}$, $I_{kr}(0) = I_{kr0}$, $I_{kn}(0) = I_{kn0}$, and $A(0) = A_0$. Here " $\dot{}$ " denotes the first derivative with respect to time t.

3. Model analysis

3.1. Positivity and boundedness of the model solutions

It is easy to show that all solutions $S(t)$, $S_p(t)$, $I_d(t)$, $I_{dp}(t)$, $I_{kr}(t)$, $I_{kn}(t)$, and $A(t)$ of the system of equations (3)–(9), which basically represent human populations, starting with non-negative initial values will remain non-negative for all the time. Moreover, adding all the equations in (3)–(9) yields

$$\dot{N}(t) = \pi - \mu N(t) - \delta A(t), \tag{10}$$

which implies

$$\dot{N}(t) + \mu N(t) \leq \pi. \tag{11}$$

Now, by applying a Theorem of Birkhoff and Rota [15] on differential inequalities, to solve (11), we have

$$0 \leq N(t) \leq \frac{\pi}{\mu} + \left(N(0) - \frac{\pi}{\mu} \right) e^{-\mu t}, \quad t \geq 0. \tag{12}$$

Taking the limit as $t \to \infty$ of equation (12) yields $0 \leq N(t) \leq \frac{\pi}{\mu}$. This shows that all solutions $S(t)$, $S_p(t)$, $I(t)$, $I_{dp}(t)$, $I_{kr}(t)$, $I_{kn}(t)$, and $A(t)$ of the system of equations (3)–(9) are bounded on a maximal domain of existence given by

$$\Omega_m = \left\{ (S, S_p, I_d, I_{dp}, I_{kr}, I_{kn}, A) \in \mathbb{R}^7_+ : S + S_p + I_d + I_{dp} + I_{kr} + I_{kn} + A \leq \frac{\pi}{\mu} \right\}.$$

This shall therefore represent the admissible biological and feasible region of our model. The region Ω_m is a closed set where the model's key features such as the existence, the positivity, the uniqueness and the continuation of the solutions hold. One can show, using results in [16], that the feasible region Ω_m is positively invariant and attracting. Thus, it is sufficient to study the dynamics of the model in Ω_m.

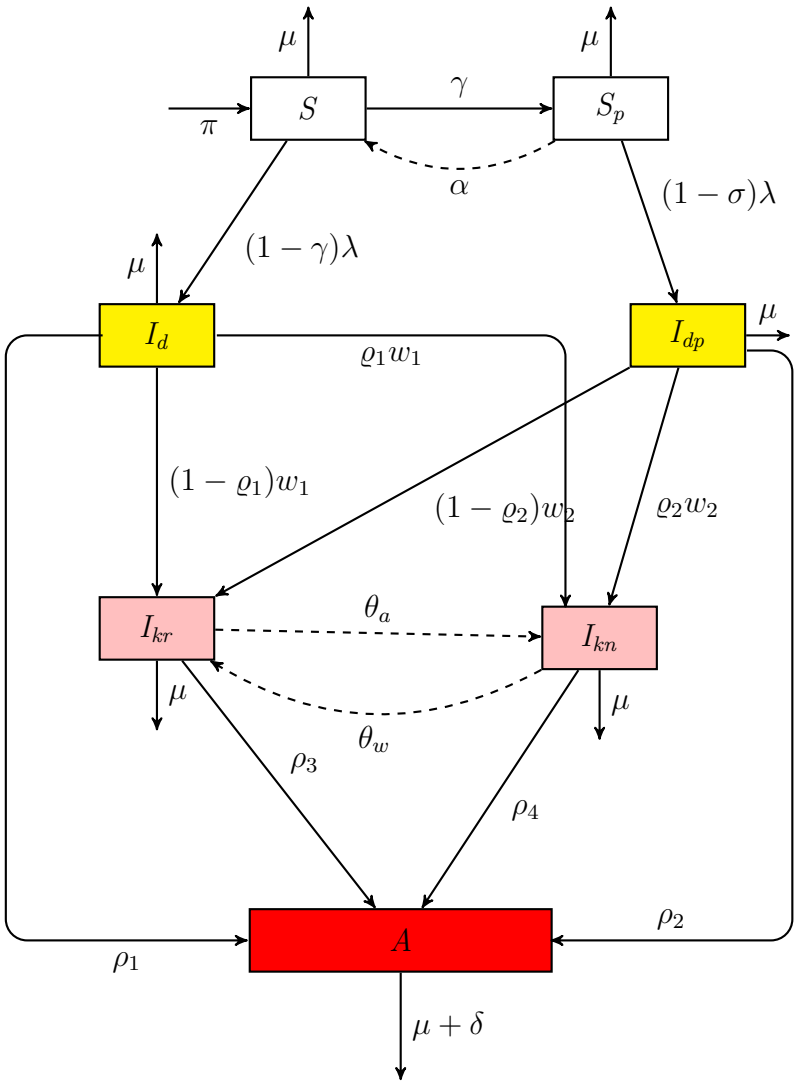

Figure 1: The schematic diagram that depicts the HIV infection dynamics between the seven subclasses. The dashed arrows depict the relapse on the preceding behaviour.

3.2. Equilibrium points of the model

The system (3)–(9) has two equilibrium points, the disease free equilibrium (DFE) point given by

$$\mathcal{E}_0 = (S_0, S_{p0}, I_{d0}, I_{dp0}, I_{kr0}, I_{kn0}, A_0) = \left(\frac{\pi(\alpha+\mu)}{\mu(\gamma+\alpha+\mu)}, \frac{\gamma\pi}{\mu(\gamma+\alpha+\mu)}, 0, 0, 0, 0, 0\right), \quad (13)$$

and the endemic equilibrium (EE) point given by

$$\mathcal{E}^* = (S^*, S_p^*, I_d^*, I_{dp}^*, I_{kr}^*, I_{kn}^*, A^*), \quad (14)$$

where

$$
\begin{aligned}
S^* &= \frac{(\alpha+\mu)\pi+(1-\sigma)\pi\lambda^*}{\Theta_2\lambda^{*2}+\Theta_1\lambda^*+\Theta_0} = \frac{E\pi}{F}, && (15)\\
S_p^* &= \frac{\gamma\pi}{\Theta_2\lambda^{*2}+\Theta_1\lambda^*+\Theta_0} = \frac{\gamma\pi}{F}, && (16)\\
I_d^* &= \frac{(1-\gamma)}{\rho_1+w_1+\mu}\frac{\lambda^* E\pi}{F}, && (17)\\
I_{dp}^* &= \frac{(1-\sigma)}{\rho_2+w_2+\mu}\frac{\lambda^*\gamma\pi}{F}, && (18)\\
I_{kr}^* &= \Delta_1^r\frac{(1-\gamma)}{\rho_1+w_1+\mu}\frac{\lambda^* E\pi}{F}+\Delta_2^r\frac{(1-\sigma)}{\rho_2+w_2+\mu}\frac{\lambda^*\gamma\pi}{F}, && (19)\\
I_{kn}^* &= \Delta_1^n\frac{(1-\gamma)}{\rho_1+w_1+\mu}\frac{\lambda^* E\pi}{F}+\Delta_2^n\frac{(1-\sigma)}{\rho_2+w_2+\mu}\frac{\lambda^*\gamma\pi}{F}, && (20)\\
A^* &= \frac{(\rho_1+\rho_3\Delta_1^r+\rho_4\Delta_1^n)(1-\gamma)}{(\mu+\delta)(\rho_1+w_1+\mu)}\frac{\lambda^* E\pi}{F}+\frac{(\rho_2+\rho_3\Delta_2^r+\rho_4\Delta_2^n)(1-\sigma)}{(\mu+\delta)(\rho_2+w_2+\mu)}\frac{\lambda^*\gamma\pi}{F}, && (21)
\end{aligned}
$$

with

$$
\begin{aligned}
\Theta_2 &= (1-\sigma)(1-\gamma), \quad \Theta_1=(\alpha+\mu)(1-\gamma)+(1-\sigma)(\gamma+\mu), \quad \Theta_0=\mu(\mu+\alpha+\gamma),\\
\Delta_i^r &= \frac{w_i(\theta_w+(1-\varrho_i)(\rho_4+\mu))}{(\rho_4+\mu)(\rho_3+\mu+\theta_a)+\theta_w(\rho_3+\mu)}, \; \Delta_i^n=\frac{w_i(\theta_a+\varrho_i(\rho_3+\mu))}{(\rho_4+\mu)(\rho_3+\mu+\theta_a)+\theta_w(\rho_3+\mu)}.
\end{aligned}
$$

Substituting equations (15)–(21) for the force of infection λ^* in equation (2), we obtained

$$P(\lambda^*)=\lambda^*(C_2\lambda^{*2}+C_1\lambda^*+C_0)=0, \tag{22}$$

where

$$
\begin{aligned}
C_0 &= 1-\mathcal{R}_0,\\
C_1 &= \frac{1-\sigma}{\gamma+\alpha+\mu}+\frac{\alpha+\mu}{\gamma+\alpha+\mu}\frac{(1-\gamma)}{\rho_1+w_1+\mu}\left(1+\Delta_1^r+\Delta_1^n+\frac{(\rho_1+\rho_3\Delta_1^r+\rho_4\Delta_1^n)}{(\mu+\delta)}\right)+\\
&\quad \frac{\gamma}{\gamma+\alpha+\mu}\frac{(1-\sigma)}{\rho_2+w_2+\mu}\left(1+\Delta_2^r+\Delta_2^n+\frac{(\rho_2+\rho_3\Delta_2^r+\rho_4\Delta_2^n)}{(\mu+\delta)}\right)-\\
&\quad \frac{(1-\gamma)(1-\sigma)}{(\gamma+\alpha+\mu)(\rho_1+w_1+\mu)}(1+\eta_2\Delta_1^r)\\
C_2 &= \frac{1-\sigma}{\gamma+\alpha+\mu}\frac{(1-\gamma)}{\rho_1+w_1+\mu}\left(1+\Delta_1^r+\Delta_1^n+\frac{(\rho_1+\rho_3\Delta_1^r+\rho_4\Delta_1^n)}{(\mu+\delta)}\right).
\end{aligned}
$$

From (22), $\lambda^*=0$ corresponds to the DFE point and $\lambda^*=((-C_1+\sqrt{C_1^2-4C_2C_0})/2C_2)$ corresponds to endemic equilibrium, which exists only when $\lambda^*>0$, that is $\mathcal{R}_0>1$. This result is summarized below.

Lemma 1. *The endemic equilibrium point of the model exists only when* $\mathcal{R}_0>1$.

3.3. The control reproduction number $\mathcal{R}_0$

The average number of secondary infections that would produce a typical infected individual in a purely susceptible population is known as the control reproduction number, denoted by $\mathcal{R}_0$. This number is a very useful parameter in epidemic disease models analyses as it represents the epidemic threshold. Thus, $\mathcal{R}_0$ is often used to suggest conditions under which the epidemic's outbreak will occur. The parameter $\mathcal{R}_0$ is mathematically defined as the spectral radius of the next generation matrix [17]. For our system (3)–(9), the parameter $\mathcal{R}_0$ is given by

$$\mathcal{R}_0 = e_\gamma^* \mathcal{R}_1 + e_\sigma^* \mathcal{R}_2, \tag{23}$$

where

$$\begin{aligned}
e_\gamma^* &= \frac{(1-\gamma)(\alpha+\mu)}{(\gamma+\alpha+\mu)}, \qquad e_\sigma^* = \frac{(1-\sigma)\gamma}{(\gamma+\alpha+\mu)}, \\
\mathcal{R}_1 &= \frac{c\eta_1}{(\rho_1+\mu+w_1)} + \frac{c\eta_3(\theta_w + (1-\varrho_1)(\rho_4+\mu))w_1}{(\rho_1+\mu+w_1)((\rho_4+\mu)(\rho_3+\mu+\theta_a)+\theta_w(\rho_3+\mu))}, \\
\mathcal{R}_2 &= \frac{c\eta_2}{(\rho_2+\mu+w_2)} + \frac{c\eta_3(\theta_w + (1-\varrho_2)(\rho_4+\mu))w_2}{(\rho_2+\mu+w_2)((\rho_4+\mu)(\rho_3+\mu+\theta_a)+\theta_w(\rho_3+\mu))}.
\end{aligned}$$

Examining each component of $\mathcal{R}_0$, it follows that

- $\mathcal{R}_1$ models the average number of new HIV infections generated by an infected non-PrEP user individual who does not know his/her HIV status and an infected non-PrEP user individual who now knows his/her HIV status but engaged in risky sexual activities.

- $\mathcal{R}_2$ models the average number of new HIV infections generated by an infected PrEP user individual who does not know that PrEP failed to protect him/her and infected PrEP user individual, tested HIV-positive, and who still indulges in risky sexual activities.

- The coefficient e_γ^*, $0 < e_\gamma^* < 1$, measures the effectiveness of the PrEP awareness whereas the coefficient e_σ^*, $0 < e_\sigma^* < 1$, measures the effectiveness of PrEP efficacy level. In brief, the smaller the coefficients e_γ^* and e_σ^* are, the smaller the contributions $\mathcal{R}_1$ and $\mathcal{R}_2$ have on $\mathcal{R}_0$.

3.4. Analysis of $\mathcal{R}_0$

We now carry on the model analysis investigating the impact of the variation of the model parameter values on the control reproduction number $\mathcal{R}_0$. The analysis will help in identifying the control parameters, whose an increase or decrease value would induce the spread of the disease across the population. Analysis on the parameters are very important in epidemic disease models as they can guide the design of a proper control strategy.

3.4.1. Effects of the control parameters on $\mathcal{R}_0$

We proceed by analysing the sensitivity of $\mathcal{R}_0$ with respect to the defined control parameters, γ, σ, ϱ_1, and ϱ_2.

We assess the impact of the PrEP awareness level on the new HIV infection rate by computing

$$\mathcal{T}^{\gamma}_{\mathcal{R}_0} = \lim_{\gamma \to 1} \mathcal{R}_0 = \lim_{e^*_\gamma \to 0} \mathcal{R}_0 = \frac{1-\sigma}{1+\gamma+\mu}\mathcal{R}_2 < \mathcal{R}_0, \tag{24}$$

which shows a reduction of the control reproduction number $\mathcal{R}_0$ to $\mathcal{T}^{\gamma}_{\mathcal{R}_0}$, where $\mathcal{T}^{\gamma}_{\mathcal{R}_0} < \mathcal{R}_0$. The result (24) shows that an increase in the proportion of the susceptible individuals on PrEP use can be effective in controlling the spread of HIV infection in community, but does not guarantee a total eradication of the disease. Efforts should be made to consider PrEP drugs efficacy level as well. Note that when (γ, σ) tend to $(1, 1)$ the disease is completely eradicated ($\mathcal{R}_0$ tends to zero). In addition, remark that PrEP use awareness has no impact on $\mathcal{R}_0$, when $e^*_\gamma = 1$. This condition can not be attained since it implies $\alpha + \mu = -1$, which is not possible. The contribution $\mathcal{R}_1$ into the infection progression is therefore reduced by the coefficient $e^*_\gamma < 1$. Note that when γ tends to unity (100% effective), e^*_γ tends to zero, that is, the more there are susceptible individuals on PrEP use, the more the new HIV infection rate is reduced. The coefficient e^*_γ thus measures the effectiveness of the PrEP awareness.

Next we compute

$$\mathcal{T}^{\sigma}_{\mathcal{R}_0} = \lim_{\sigma \to 1} \mathcal{R}_0 = \lim_{e^*_\sigma \to 0} \mathcal{R}_0 = e^*_\gamma \mathcal{R}_1 < \mathcal{R}_0, \tag{25}$$

to investigate the impact of the PrEP drugs efficacy level on $\mathcal{R}_0$. We note from equation (25) that a significant increase in the efficacy of PrEP drugs would result in the decline of new HIV infections ($\mathcal{T}^{\sigma}_{\mathcal{R}_0} < \mathcal{R}_0$). We also note that the coefficient $e^*_\sigma < 1$, since $e^*_\sigma = 1$ leads to $\sigma = -\frac{\alpha+\mu}{\gamma} < 0$, which is not possible. The contribution $\mathcal{R}_2$ on $\mathcal{R}_0$ is therefore reduced by the coefficient e^*_σ, so that $0 \leq e^*_\sigma < 1$. As a result, one can conclude that raising PrEP efficacy level will certainly reduce the HIV infection rate but nevertheless does not guarantee a total elimination of the disease. The factor e^*_σ thus measures the effectiveness of the PrEP efficacy.

Finally, we investigate the benefits of post-infection educational services, which implicitly should highlight the benefits of more frequent and greater scope of HIV screening programs. To do so, we compute

$$\mathcal{T}_{\mathcal{R}_0} = \lim_{(\varrho_1, \varrho_2) \to (1,1)} \mathcal{R}_0 = e^*_\gamma \lim_{\varrho_1 \to 1} \mathcal{R}_1 + e^*_\sigma \lim_{\varrho_2 \to 1} \mathcal{R}_2 = \mathcal{T}^{\varrho_1}_{\mathcal{R}_1} + \mathcal{T}^{\varrho_2}_{\mathcal{R}_2}. \tag{26}$$

Noting that $\mathcal{T}^{\varrho_1}_{\mathcal{R}_1} < \mathcal{R}_1$ and $\mathcal{T}^{\varrho_2}_{\mathcal{R}_2} < \mathcal{R}_2$, it is clear that $\mathcal{T}_{\mathcal{R}_0} < \mathcal{R}_0$. This suggests that an increase in the proportion of infected individuals who withdraw from risky sexual activities after being tested HIV positive would have a remarkable benefit in averting new HIV infections. These call for regular HIV-test schedules followed by a strict post-infection monitoring associated with elimination of HIV-related stigma, discrimination, and regulation of punitive laws and practices.

Table 1: The model parameter values ($year^{-1}$) and their interpretations

Parameter	Definition	Value (range)	Reference
γ	PrEP awareness level	$0.72\,(0-0.99)$	[18]
σ	PrEP efficacy level	$0.92\,(0.9-1.0)$	[19]
μ	Natural death rate	$0.025\,(0.01-0.025)$	[20]
δ	Disease related deaths rate	$0.33\,(0.3-0.75)$	[21, 22]
θ_w	Risky sexual withdrawal rate in I_{kn} class	0.04	Assumed
π	Recruitment rate	$0.20 \times 5 \times 10^3$	Assumed
α	Non PrEP use relapse rate	0.015	Assumed
θ_a	Risky sexual behaviour relapse rate in I_{kr} class	0.01	Assumed
ϱ_1, ϱ_2	Proportions of individuals who abstain from risky sexual activities in I_d and I_{dp} class, respectively	0.35, 0.65	Assumed
w_1	HIV screening rate in I_d class	0.30	[23]
w_2	HIV screening rate in I_{dp} class	0.45	Assumed
η_1	HIV transmission rate per contact with I_d individual	1.215	Assumed
η_2	HIV transmission rate per contact with I_{dp} individual	0.0219	[11]
η_3	HIV transmission rate per contact with I_{kr} individual	0.125	[20]
c	Average number of risky sexual acts	1.5	[24]
ρ_1, ρ_2, ρ_3, ρ_4	Progression rates to AIDS by I_d, I_{dp}, I_{kr} and I_{kn} individuals, respectively	0.074, 0.060, 0.068, 0.052	Assumed

3.4.2. Sensitivity analysis of the control parameters on $\mathcal{R}_0$

We carry on the analysis of the control reproduction number $\mathcal{R}_0$ with respect to the control parameters γ, σ, ϱ_1, and ϱ_2 using the normalised forward sensitivity index (n.f.s.i) theory [25]. Unlike the preceding analyses of $\mathcal{R}_0$, the n.f.s.i analysis helps one to classify, in the most beneficial way to the least beneficial order, the control parameters impact on the new infection rate reduction. This allows one to structure the control strategies and interventions for successful HIV infection control.

Using the definition of the n.f.s.i in [25], the sensitivity index of $\mathcal{R}_0$ with respect to the control parameters γ, σ, ϱ_1, and ϱ_2 are computed using the parameter values in Table 1. We obtained the results as follows:

$$\Gamma_{\varrho_1}^{\mathcal{R}_0} = -0.057, \qquad \Gamma_{\varrho_2}^{\mathcal{R}_0} = -0.075, \qquad \Gamma_{\gamma}^{\mathcal{R}_0} = -1.335, \qquad \Gamma_{\sigma}^{\mathcal{R}_0} = -3.314. \tag{27}$$

Note that, $\Gamma_p^{\mathcal{R}_0} > 0$ indicates that increasing the value of parameter p would result in an increase of the value of $\mathcal{R}_0$, whilst $\Gamma_p^{\mathcal{R}_0} < 0$ implies that increasing the value of p would lead to a decrease in the value of $\mathcal{R}_0$. Thus, the results (27) reveal that PrEP efficacy level σ is the most sensitive control parameter for the HIV infection transmission control, followed by the proportion of susceptible individuals on PrEP use γ, and then the proportions of the infected individuals who withdraw from risky sexual behaviour ϱ_2, and ϱ_1.

4. Stability analysis of the model equilibrium points

The control reproduction number $\mathcal{R}_0$ is very crucial to the stability conditions of the equilibrium points. We find the following:

Theorem 1. *The disease free equilibrium point $\mathcal{E}_0$ of the model is globally asymptotically stable when $\mathcal{R}_0 < 1$ and unstable $\mathcal{R}_0 > 1$.*

Theorem 2. *The model endemic equilibrium point $\mathcal{E}^*$ is globally asymptotically stable when $\mathcal{R}_0 > 1$.*

The proofs of these Theorems are standard, thus omitted.

5. Optimizing the control strategies

We now aim to investigate the optimal level of efforts and costs that would be needed to control the HIV infection progress when PrEP intervention strategy and post-infection service are implemented in a community.
We have seen from the above analysis of our model that HIV control intervention strategies that account for higher level of the controls modelled would substantially reduce the spread of HIV infection in communities and might lead to a total eradication of the infection. However, raising the controls to higher levels, as it is required, will be costly. Hence, a well-planned and efficient HIV control program implementation at minimal cost is needed. Optimal control theory can help to obtain an appropriate plan for a successful scheme.
To make use of the theory, we defined time dependent controls $u_1(t)$, $u_2(t)$, and $u_3(t)$, so that $0 \leq u_i(t) \leq 1$, for $i = 1, 2, 3$. Note that when the controls are time dependent, the disease free equilibrium no longer exists [26]. These controls are needed to model the reinforcement of PrEP use campaigns and HIV educational campaigns policies as well as PrEP drugs efficacy improvement. The time dependent controls $u_1(t)$ shall be tied to new HIV infections reduction through expansion of PrEP intake campaigns during which relevant knowledge and useful information about the benefits of using PrEP drugs as efficacious prevention method will be provided. The control $u_2(t)$ should be tied to the improvement of the efficacy level of the PrEP drugs provided. This would require government financial support to make the drugs affordable. The control $u_3(t)$ shall be tied to post-infection monitoring to ensure that the detected infected individuals withdraw from risky sexual acts. This requires frequent HIV test campaigns. The

Center for Disease Control and Prevention suggests that HIV testing in a PrEP program be conducted every three months [27].
We thus modified our system (3)–(9) to the system of equations

$$\begin{aligned}
\dot{S} &= \pi - u_1 S - (1-u_1)\lambda S + \alpha u_2 S_p - \mu S, && (28)\\
\dot{S}_p &= u_1 S - (1-u_2)\lambda S_p - (\alpha u_2 + \mu) S_p, && (29)\\
\dot{I}_d &= (1-u_1)\lambda S - w_1 I_d - (\rho_1 + \mu) I_d, && (30)\\
\dot{I}_{dp} &= (1-u_2)\lambda S_p - w_2 I_{dp} - (\rho_2 + \mu) I_{dp}, && (31)\\
\dot{I}_{kr} &= (1-\varrho_1 u_3) w_1 I_d + (1-\varrho_2 u_3) w_2 I_{dp} + \theta_w u_3 I_{kn} && (32)\\
&\quad -(\theta_a (1-u_3) + \rho_3 + \mu) I_{kr}, && (33)\\
\dot{I}_{kn} &= \varrho_1 w_1 u_3 I_d + \varrho_2 w_2 u_3 I_{dp} + \theta_a (1-u_3) I_{kr} - (u_3 \theta_w + \rho_4 + \mu) I_{kn}, && (34)\\
\dot{A} &= \rho_1 I_d + \rho_2 I_{dp} + \rho_3 I_{kr} + \rho_4 I_{kn} - (\mu + \delta) A, && (35)
\end{aligned}$$

with the initial conditions $S(0) = S_0$, $S_p(0) = S_{p0}$, $I_d(0) = I_{d0}$, $I_{dp}(0) = I_{dp0}$, $I_{kr}(0) = I_{kr0}$, $I_{kn}(0) = I_{kn0}$, and $A(0) = A_0$.
We further formulate an objective functional $J = J(u_1, u_2, u_3)$ given by

$$J(u_1, u_2, u_3) = \min_{u_1, u_2, u_3} \int_0^{t_f} \left[a_1 I_d + a_2 I_{dp} + a_3 I_{kr} + b_1 u_1^2 + b_2 u_2^2 + b_3 u_3^2 \right] dt, \qquad (36)$$

subject to the state system (28)–(35), where t_f is the final time of the control schedule and the positive coefficients a_1, a_2, a_3, b_1, b_2, and b_3 are balancing cost factors that transform the integral into money expended over a finite time. The objective functional $J(u_1, u_2, u_3)$ is formulated such that the costs of infection $a_1 I_d$, $a_2 I_{dp}$, and $a_3 I_{kr}$ are linear functions, whereas the cost on the controls policies $b_1 u_1^2$, $b_2 u_2^2$ and $b_3 u_3^2$ are non-linear and take quadratic forms. Note that this is consistent with other literature on optimal control applied to epidemic disease models [28, 29].
Our endeavour involves minimizing the populations of infected individuals (I_d,I_{dp}, and I_{kr}) at the risk of infecting other uninfected individuals, with the appropriate costs ($b_1 u_1^2$, $b_2 u_2^2$, and $b_3 u_3^2$) allocated onto each activity. In other words, we seek the optimal control triplet (u_1^*, u_2^*, u_3^*) such that

$$J(u_1^*, u_2^*, u_3^*) = \min \left\{ J(u_1, u_2, u_3) | (u_1, u_2, u_3) \in \mathcal{U} \right\}, \qquad (37)$$

where $\mathcal{U} = \left\{ u = (u_1, u_2, u_3) \in L^1[0, t_f],\ 0 \le u_i \le 1,\ i = 1, 2, 3 \right\}$, is the set of all possible control triplets satisfying (36). Note that $u_i(t)$, $0 \le t \le t_f$, are bounded and Lebesgue integrable.
The necessary conditions of existence of such triplets have been studied in [30] and [31]. Using Pontryagin's maximum principle [32], the optimality problem (system of equations (28)–(37)) is converted into an equivalent problem, that is, a problem of minimizing a pointwise Hamiltonian $\mathcal{H}$, with respect to u_1, u_2, and u_3, given by

$$\mathcal{H} = a_1 I_d(t) + a_2 I_{dp}(t) + a_3 I_{kr}(t) + b_1 u_1^2(t) + b_2 u_2^2(t) + b_3 u_3^2(t) + \sum_1^7 \lambda_j \dot{G}_j(t), \qquad (38)$$

where $G_j(t)$ corresponds to the j^{th} state variable in the system (28)–(35), with the corresponding adjoint (or co-state) λ_j, respectively, and solutions of the differential equations

$$\begin{aligned}
\frac{d\lambda_1}{dt} &= (\lambda_1-\lambda_2)+\lambda(1-u_1)(\lambda_1-\lambda_3)+\lambda_1\mu, && (39)\\
\frac{d\lambda_2}{dt} &= \alpha u_2(\lambda_2-\lambda_1)+(1-u_2)\lambda(\lambda_2-\lambda_4)+\lambda_2\mu, && (40)\\
\frac{d\lambda_3}{dt} &= -a_1+\frac{c\eta_1 S}{N}(1-u_1)(\lambda_1-\lambda_3)+\frac{c\eta_1 S_p}{N}(1-u_2)(\lambda_2-\lambda_4) && (41)\\
&+ \varrho_1 w_1 u_3(\lambda_5-\lambda_6)+w_1(\lambda_3-\lambda_5)+(\lambda_3-\lambda_7)\rho_1+\lambda_3\mu, && (42)\\
\frac{d\lambda_4}{dt} &= -a_2+\frac{c\eta_2 S}{N}(1-u_1)(\lambda_1-\lambda_3)+\frac{c\eta_2 S_p}{N}(1-u_2)(\lambda_2-\lambda_4) && (43)\\
&+ \varrho_2 w_2 u_3(\lambda_5-\lambda_6)+w_2(\lambda_4-\lambda_5)+(\lambda_4-\lambda_7)\rho_2+\lambda_4\mu, && (44)\\
\frac{d\lambda_5}{dt} &= -a_3+\frac{c\eta_3 S}{N}(1-u_1)(\lambda_1-\lambda_3)+\frac{c\eta_3 S_p}{N}(1-u_2)(\lambda_2-\lambda_4) && (45)\\
&+ \theta_a(1-u_3)(\lambda_5-\lambda_6)+(\lambda_5-\lambda_7)\rho_3+\lambda_5\mu, && (46)\\
\frac{d\lambda_6}{dt} &= \theta_w u_3(\lambda_6-\lambda_5)+(\lambda_6-\lambda_7)\rho_4+\lambda_6\mu, && (47)\\
\frac{\lambda_7}{dt} &= (\mu+\delta)\lambda_7, && (48)
\end{aligned}$$

with the transversality conditions $\lambda_j(t_f)=0$, $j=1,\ldots,7$.
The adjoint system (39)–(48) is obtained from Pontryagin's maximum principle [32] by computing

$$\frac{d\lambda_j}{dt}=-\frac{\partial\mathcal{H}}{\partial G_j}, \text{ where } \quad G_j=[S,S_p,I_d,I_{dp},I_{kr},I_{kn},A],\ j=1,\ldots,7.$$

Using the existence results from Corollary 4.1 in [30], we state the following theorem

Theorem 3. *The optimal control triplet (u_1^*,u_2^*,u_3^*) which minimizes the optimal functional over the admissible set $\mathcal{U}$ is given by*

$$\begin{aligned}
u_1^* &= \min\left\{1,\max\{0,\hat{u}_1\}\right\}, && (49)\\
u_2^* &= \min\left\{1,\max\{0,\hat{u}_2\}\right\}, && (50)\\
u_3^* &= \min\left\{1,\max\{0,\hat{u}_3\}\right\}, && (51)
\end{aligned}$$

where

$$\begin{aligned}
\hat{u}_1 &= \frac{(c\eta_1 I_d^*+c\eta_2 I_{dp}^*+c\eta_3 I_{kr}^*)S^*(\lambda_1-\lambda_3)}{2b_1(S^*+S_p^*+I_d^*+I_{dp}^*+I_{kr}^*+I_{kn}^*+A^*)}+\frac{(\lambda_1-\lambda_2)S^*}{2b_1}, && (52)\\
\hat{u}_2 &= \frac{(c\eta_1 I_d^*+c\eta_2 I_{dp}^*+c\eta_3 I_{kr}^*)S_p^*(\lambda_2-\lambda_4)}{2b_2(S^*+S_p^*+I_d^*+I_{dp}^*+I_{kr}^*+I_{kn}^*+A^*)}+\frac{\alpha(\lambda_2-\lambda_1)S_p^*}{2b_2}, && (53)\\
\hat{u}_3 &= \frac{(\varrho_1 w_1 I_d^*+\varrho_2 w_2 I_{dp}^*+\theta_a I_{kr}^*+\theta_w I_{kn}^*)(\lambda_5-\lambda_6)}{2b_3}, && (54)
\end{aligned}$$

S^*, S_p^*, I_d^*, I_{dp}^*, I_{kr}^*, I_{kn}^*, A^* and λ_j, $j = 1, \ldots, 7$ are solutions of (28)–(35) and (39)–(48), respectively.

PROOF. Results in equations (52)–(54) are obtained by differentiating the Hamiltonian $\mathcal{H}$ with respect u_1, u_2, and u_3 and then equate the resulting expressions to zero, that is

$$\frac{\partial \mathcal{H}}{\partial u_1} = 0, \qquad \frac{\partial \mathcal{H}}{\partial u_2} = 0, \qquad \frac{\partial \mathcal{H}}{\partial u_3} = 0, \tag{55}$$

then solve for $u_1 = \hat{u}_1$, $u_2 = \hat{u}_2$, and $u_3 = \hat{u}_3$. Next, taking into account the boundary conditions defined in $\mathcal{U}$, one can easily derive the result in (52)–(54).
Due to the priori boundedness of the states system (28)–(35) and the adjoints system (39)–(48), and the resulting Lipschitz structure of the ODEs, the uniqueness of the optimal control is obtained for the small time t_f. The uniqueness of the optimal control triplet (u_1^*, u_2^*, u_3^*) follows from the uniqueness of the optimality system, which consists of the fourteen ordinary differential equations (the states system and (28)–(35) the corresponding adjoint system (39)–(48)) together with the control characteristics. There is a restriction of the length of the time interval $[0, t_f]$ in order to guarantee the uniqueness of the optimality system. This smallest restriction of the length on the time is due to the opposite time orientation of the adjoints system; the state system has initial values and the corresponding adjoints system has final values.

6. Numerical results

We carried out the model analysis to numerically solve the optimality system. We do this to explore and get better understanding of the potential effects of the optimal control strategies on HIV burden. We used a forward-backward version of fourth order Runge-Kutta scheme. The algorithm is described and presented in [33] as follows: given initial values for the state variables S_0, S_{p0}, I_{d0}, I_{dp0}, I_{kr0}, I_{kn0}, and A_0 and initial estimated values for the control parameters, u_1^0, u_2^0, and u_3^0, the states system (28)–(35) is solved forward in time, and then using the resulting state values and the given final time, the adjoint system (39)–(48) is then solved backward (and this because of the traversality conditions). Furthermore, using both state and adjoints values obtained from the iterations, the optimal triplet in (52)–(54) are updated. This process is repeated until the current states, adjoints, and the optimal control triplet values converge sufficiently.
For a comprehensive and successful HIV PrEP implementation program, we suggest to one to apply our modelled assumptions to a manageable size of populations (who are at high risk of HIV infection); and this, simply for better follow-up and frequent HIV screening to ensure that patients taking PrEP and who further have tested HIV-positive, immediately stop PrEP intake and be offered post-infection counselling services. We also suggest to consider population of individuals who are sufficiently mature to receive PrEP adherence lessons (and who are sexually active). From report [21], individuals aged between 15 and 49 years are more qualified. We thus defined an initial populations size given as follows: $S_0 = 3600$, $S_{p0} = 450$, $I_{d0} = 225$, $I_{dp0} = 50$, $I_{kr0} = 60$, $I_{kn0} = 0$,

and $A_0 = 0$.
Report in 2012 on cost-effectiveness of PrEP use for HIV infection in South Africa [34] estimated that HIV care with PrEP program cost to be US$9890 per years of life save, compared to US$7280 cost for HIV care without PrEP. This gives $b_1 = 7280$ and $b_2 = 9890$. It is well known that pre-infection care is generally cheaper than post-infection care. On that score, we assumed that the cost $u_3(t)$ allocated to post-infection care is greater than the costs $u_1(t)$ and $u_2(t)$, which are cost tied to pre-infection cares. We then assumed $b_3 = b_1 + b_2 = 17170$. Intuitively, the corresponding efforts on each duty are chosen to be $a_1 = 200$, $a_2 = 400$ and $a_3 = 600$, respectively. The parameter values used are obtained from the few available literature related to PrEP HIV program. These values are summarized in Table 1. It is worth noting that the parsimonious assumptions of the other parameters values fed from the scarcity and limited data on PrEP use, at the moment. Nevertheless, we portray that these values are taken in the realistic range for numerical simulations purpose.

The simulation results showing the time evolution of the infected populations $I_d(t)$, $I_{dp}(t)$, and $I_{kr}(t)$ and the susceptible non-PrEP users $S(t)$ for situations where optimal controls are considered (solid line) and where they are not (dashed line) are presented in Figure 2; while those of the controls $u_1(t)$, $u_2(t)$, and $u_3(t)$ are shown in Figure 3.
From Figure 2(a), we observe a great decrease of the number of susceptible non-PrEP users (at risk of becoming infected) at the initial times of PrEP program. However, the results indicate that without optimal control the susceptible non-PrEP users would resume to high risky behaviour after the first 5 years, whereas a significant risky behaviour reduction is marked when optimal control is considered. The profile of the control tied to the increase of PrEP awareness scopes $u_1(t)$ is presented in Figure 3(a). From the result, we observe that the control $u_1(t)$ monotonously remains at the upper bound till the final time. This suggests that PrEP awareness campaigns (during which comprehensive PrEP use policies and PrEP use benefits knowledge are given by recruited PrEP experts) are needed to be maintained highly consistent from the initial time till the final time of the PrEP program.
In Figure 2(b)-(c), the time evolution of the infected non-PrEP users and infected PrEP users are presented. In both figures, we observe a significant decrease of the number of the infected individuals when optimal control is applied, from the initial implementation time of PrEP program, which progressively tends to zero (that is the infection free point). On the other hand, we observe that without optimal control the number of infected individuals in both classes (I_d and I_{dp}) steeply increases, reach its peak value and then drops progressively to zero. These results clearly indicate that with application of optimal control a much less time will be taken to eradicate the infection from the population. With optimal control, we observe from Figure 2(b) that the infection free point is reached within 30 years while from Figure 2(c), this is reached within 20 years. The profile of the control tied to PrEP efficacy level improvement $u_2(t)$ is presented in Figure 3(b). The control monotonously remains at the upper bound till the final time. This reveals that PrEP efficacy is needed to be maintained at higher level from the starting point of the PrEP program till the end in order to get an effective decline of

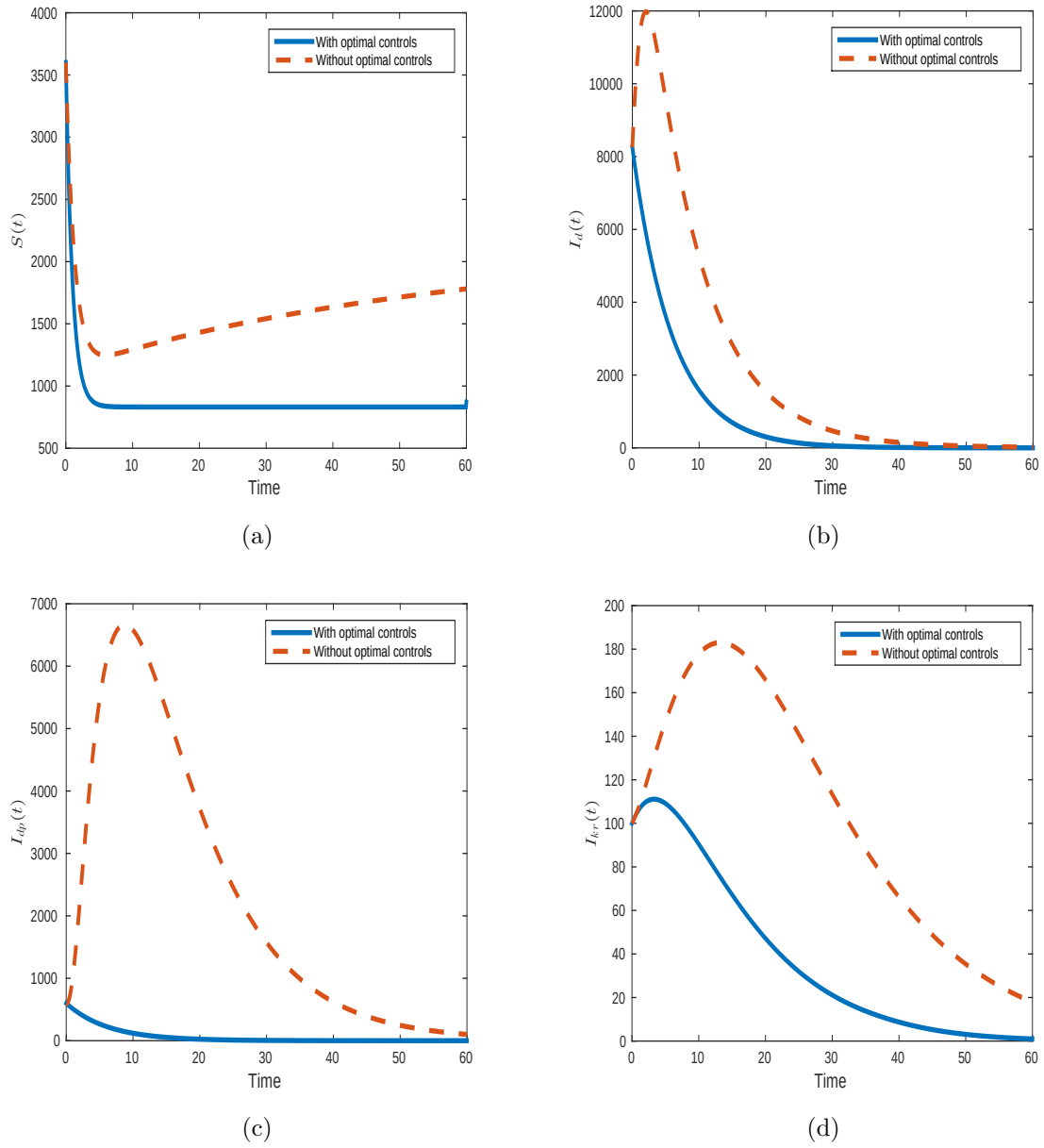

Figure 2: Time evolution of the non-PrEP user $S(t)$ and the infected $I_d(t)$, $I_{dp}(t)$ and $I_{kr}(t)$ populations over time with the given parameters and the initial state variables values.

new HIV infections cumulative in the population.
In Figure 2(d), we illustrate the time evolution of the population of the infected individuals aware of their HIV status and who have not changed their risky sexual behaviour. The results show a substantial reduction of the number of infected individuals indulged in risky sexual behaviour when optimal control is applied compared to the case where it is not. With optimal control, we observe that the peak value is reached within the first 4 years while in the case without optimal control this is reached after 10 years. Comparing the peaks values obtained in both cases, we have $r \approx 0.57$, which infers

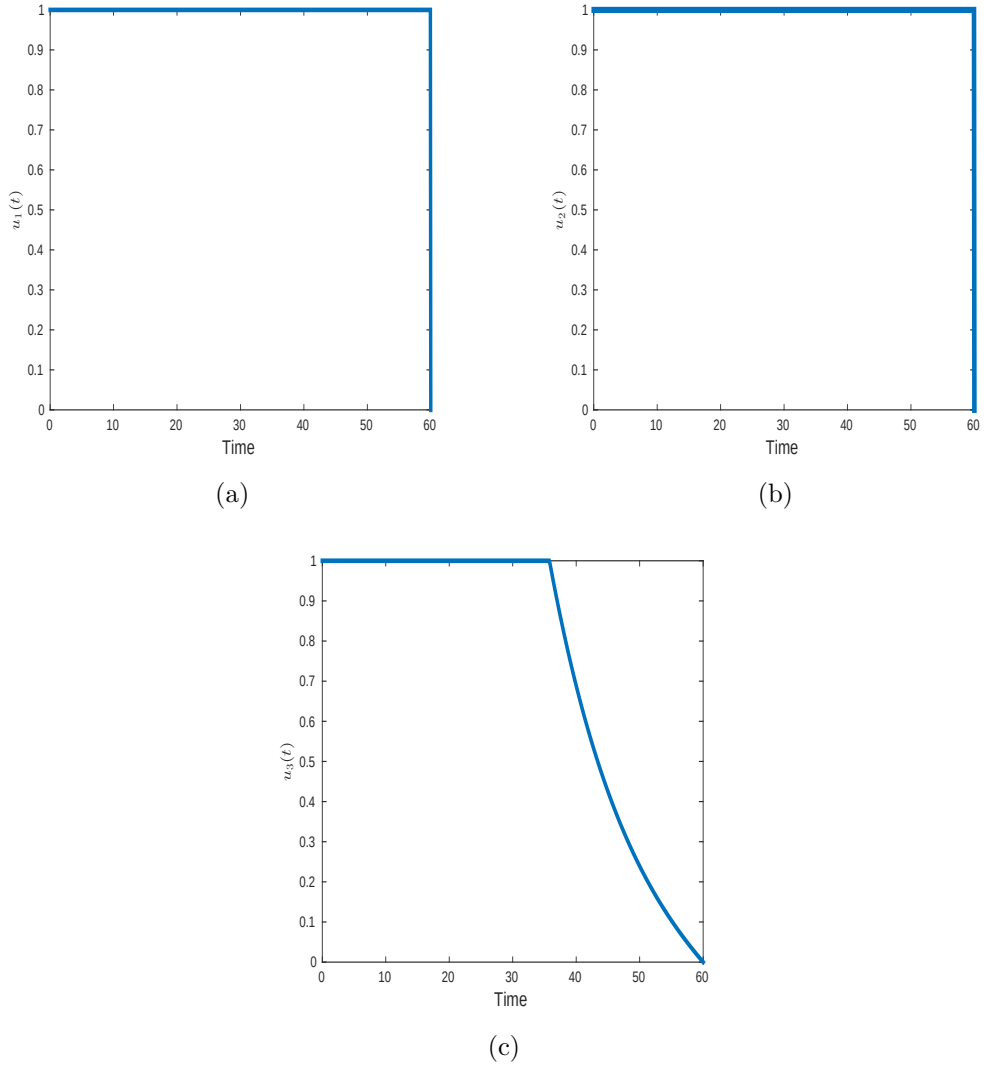

Figure 3: Numerical results of the optimal controls $u_1(t)$, $u_2(t)$, and $u_3(t)$ over time.

57% risk reduction when optimal control is applied. The profile of the control tied to the reinforcement of post-infection educational service $u_3(t)$, presented in Figure 3(c), monotonously remains at the upper bound in the first 35 years and then hyperbolically drops to zero. This suggests that the post-infection monitoring should be maintained at the high level in the first 40 years.

7. Discussion and Conclusion

PrEP drugs use as HIV infection prevention intervention has been proven effective in high risk infection settings (commercial sex workers, intravenous drugs users, homeless people, or prison inmates). In this article, a homogeneous population at high risk of HIV infection and where PrEP drugs are accessible is considered to analyse the impact of PrEP drugs use and post-infection supports on HIV infection prevalence. A math-

ematical model that subdivides the population with respect to their HIV status and their health precaution care taken is developed and analysed. The infection threshold, i.e the model control reproduction number ($\mathcal{R}_0$) is computed and qualitatively analysed to gain insights into the infection dynamics. The proportion of the susceptible individuals on PrEP use, the efficacy level of the drugs, and the proportion of the infected individuals withdrawn from risky sexual contact are the key control factors targeted for the model analysis. Sensitivity analysis of the variation of the control factors values on $\mathcal{R}_0$ was performed and the results suggest that new HIV infections reduction would be significant when PrEP efficacy level is maintained at high level, followed by the proportion of susceptible individuals on PrEP use and then the number of infected individual withdrawn from risky sexual behaviour. Next, $\mathcal{R}_0$ is used to analyse the stability conditions of the model equilibrium points. Results show that when $\mathcal{R}_0 < 1$, the disease free equilibrium is stable and unstable otherwise; and when $\mathcal{R}_0 > 1$, the endemic equilibrium point is globally asymptotically stable. Furthermore, optimal control theory using Pontryagin's maximum principle is applied to our model introducing time dependent control parameters for cost effective analysis. The optimality system obtained is analysed and numerical simulations are performed. The results suggest that new HIV infections reduction would be effective through PrEP intervention when time dependent control is considered. These results indicate that with time dependent controls (optimal controls) a much less time would be taken to reduce new HIV infections in the population. The controls tied to the enlargement of PrEP use awareness scopes and to the improvement of PrEP efficacy are to be maintained at the high level from the initial time of the PrEP program until the end if the PrEP intervention is to be effective. For the control tied to the post-infection policies reinforcement, the simulations suggest that effective and prompt post-infection education services should be provided to ensure maximum change of risk behavioural in the first 35 years.
We suggest more HIV healthcare experts recruitment for sufficient and effective post-infection monitoring, intensive comprehensive PrEP drugs intake policies communication, zero tolerance of application of HIV-positive individuals stigmatization and discrimination punitive laws, face-to-face consultation for individuals with low literacy to build an ongoing dialogue regarding the benefit of risky behavioural reduction, and consistent reminder of additional preventive methods (such as condoms use, faithfulness, less sexually active partners acquisition) to the PrEP drugs intake or consistence and timely use of PrEP drugs.

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Chapter 5

Conclusions and recommendation

This research study is focused on developing and analysing mathematical HIV models, which comprise systems of ordinary differential equations that capture the dynamics of HIV infection under PrEP intervention and PrEP in combination with other HIV control approaches. The analysis and the results obtained from these models are to contribute to the ongoing investigations and understanding of the potential ability of PrEP use by HIV-uninfected individual to reduce the likelihood of sexual HIV infection acquisition and outline the benefits of combining PrEP with HIV infection control intervention such as early ART and risk reduction educational in post-HIV infection intervention.

Underlying development surrounding the origin and progression of HIV/AIDS disease were presented. Recent advances in HIV infection prevention and treatment approaches were also reviewed as well as the current HIV prevention strategies (use of ARV for PrEP). Our study tapped into the current prevention intervention strategies and putting into context the benefits of combining these and other already existing strategies.

In chapter 2, we formulated a mathematical PrEP model by extending the standard SIR model incorporating two key PrEP control factors, that is, PrEP efficacy and PrEP use awareness for analysis. The model analysis was carried out and conditions under which the endemicity level of HIV infection can be brought under control ($\mathcal{R}_0 < 1$) with PrEP intervention were established. Four hypothetical PrEP strategies, characterizing the quality of both PrEP factors (low/high

PrEP use awareness and low/high PrEP efficacy) were thus considered. The results show that in most of these strategies considered, the model epidemic threshold $\mathcal{R}_0$ stayed above unity except for the strategy where high PrEP awareness ($> 85\%$) and high PrEP efficacy ($> 85\%$) is implemented. This implies that the strategy of high PrEP awareness and high PrEP efficacy significantly reduces HIV incidence better than any other strategy. Moreover, we note that even at high levels of awareness, $\mathcal{R}_0$ remains close to unity, which indicates that PrEP intervention alone as a mono-strategy may not continuously keep the HIV burden under check. This observation reveals the necessity of associating PrEP implementation with other forms of intervention such as effective use of male and female condoms, ARV treatment intervention and home-based care. The study in [68] reported that PrEP efficacy of at least 80 percent was able to reduce the basic reproduction ratio below unity. Our results in this study with parameter values from the South African HIV statistics [74] are in agreement with those results.
Note, however, that maintaining PrEP awareness and PrEP efficacy at such high levels in the long-term would pose a big challenge, since it would demand considerable effort and funds as well as sufficient recruitment and effective training of PrEP drugs' providers for proper monitoring and follow up of PrEP users, plus the subsidization of the price of high efficacy PrEP drugs. On the other hand, this would require a strict adherence of individuals to the PrEP drug uptake and effective monitoring efforts for appropriate follow up of PrEP users.

In chapter 3, we modified the PrEP model incorporating ARV use for treatment to assess the impact of combining PrEP intervention as a pre-infection control and ARV use as a post-infection control in the fight against new HIV infections. We also considered drug resistance, which is one of the crucial factors that potentially impedes the overall effectiveness of PrEP intervention. PrEP drug resistance often emerges from PrEP used by pre-infected individuals. Thus, a new class of infected individuals was incorporated into the modified model. The model analysis showed that HIV incidence would be more significantly reduced when PrEP and ARVs interventions are concurrently implemented at high rates, compared to PrEP or ARV intervention as a single control strategy. Similar observations were also reported from other studies [59, 92, 129]. A mathematical model was developed and analysed in [93] to access the impact of the current ARV use as a pre-exposure vaccine in controlling HIV infection. Their

results also recommended a combination of PrEP and ART interventions in the fight to new HIV infections. However, the authors did not consider PrEP drug resistance, which is one of the most important factors that usually impede PrEP efficacy. Our model results also reveal that the increase in the number of misdiagnosed infected individuals on PrEP use could be a key driver of the HIV infection spread. Moreover, the results exhibited that the contribution of PrEP drug resistance to the spread of HIV infection would partially depend on the duration of PrEP use by the already-infected individuals. This demands regular HIV screening (at least every 3 months as recommended by CDC), as well as proper monitoring and follow-up during the pre- and post-randomized PrEP prescription protocols.

In Chapter 4, post-infection educational support service (for risk behaviour change in the detected infected individuals) is introduced into the PrEP model. Discontinuity of PrEP intake was incorporated. In the first part, investigation of the steady-state conditions of the model equilibrium points were carried out while in the second part, optimal control theory using Pontryagins Maximum Principle was applied to the model. Time dependent control variables (policies) for cost effective analysis were thus formulated. The results highlighted that a combination of PrEP intervention and post-HIV infection educational support service is very effective in minimizing the population of infected individuals indulging in risky sexual behaviour and hence resulting in a great decline in HIV incidence and prevalence. The results also demonstrated that with optimal controls, new HIV infections will be eradicated in a much shorter time and with cost saving benefits, compared to the case without optimal controls. The simulations show that the control policies must be maintained constantly at high levels with maximum efforts deployed in post-HIV infection support from the initial time until the end.

In summmary our study in this thesis seems to suggest that

- PrEP intervention with low PrEP awareness and low PrEP drugs efficacy may to some extend reduce the endemicity level of HIV infection but would remain an ineffective approach to reach the total eradication target.
- High PrEP awareness that optimizes adherence among PrEP users and high PrEP efficacy are urgently needed if the cumulative number of new HIV infections is to be reduced.

- PrEP intervention alone (even at high levels) cannot mitigate the HIV infection burden in the long-term just like other pre-existing intervention strategies. The PrEP control may be much more beneficial if used in combination with other effective HIV control strategies.

- PrEP for prevention and ART for treatment (when both are concurrently implemented) would significantly reduce HIV incidence and might possibly led to zero new HIV infections.

- Combination of PrEP intervention with risk behaviour reduction education (which seeks to minimize the population of infected individuals indulging in risky sexual behaviour) would have a great impact in declining HIV incidence and prevalence. The decline is achievable in a much shorter time and with cost saving benefits when optimal controls are considered, compared to the case without optimal controls.

Our findings in this project have great implications for ongoing investigations and planning of HIV control and effective PrEP and PrEP in combination with other pre-existing prevention approaches implementation for HIV infection control. In addition to these findings, we recommend that if HIV infection is to be eradicated through effective PrEP intervention and PrEP associated with other strategies, intensive PrEP use awareness through media and other means of communication, introduction of PrEP use knowledge and distribution of PrEP guideline books in high learning institutions as well as public and recreation places must take place for maximum awareness of PrEP protection benefits among young adults. Before an individual begins PrEP, we recommend an initial 30 day follow up visit to assess the eligibility, commitment, safety, and effective use of PrEP drugs, then a prescription for 60 days, after which, sexual transmission infection screening and HIV test should be performed. This could help to reduce the occurrence of drug resistance. We also recommend a large number of HIV healthcare expert recruitment for sufficient and effective monitoring and a monthly home-based discussion and follow up for individuals with low literacy. In addition, there should be a consistent reminder of additional preventive methods (such as condoms use, faithfulness, less sexually active partners acquisition) to the PrEP drugs intake or consistence and timely use of PrEP

drugs. We also recommend establishment of regulations against illegal and unlicensed PrEP drugs distribution to avoid provision of fake PrEP drugs. We suggest the solicitation of medical insurance organisations and governmental health stakeholder involvement for financial support to ensure that the price of high efficacy PrEP drugs is subsidized. We also suggest provision of tools and devices for reminders and timely intake of PrEP drugs. Early enrolment into ART of individuals whom PrEP failed to protect and those who are diagnosed pre-infected before PrEP is crucial. We recommend promotion of community empowerment, peer education, promotion of minimum sexual partners, identification of hidden sexual workers settings, enlargement of HIV voluntary counselling and testing scopes, distribution of HIV heath educational materials and guidelines.

We acknowledge that the models developed and analysed in this thesis could not capture all the important social factors intervening in HIV infection dynamics under control of PrEP and PrEP in combination with ART interventions and risk reduction educational services. Thus, our findings cannot be regarded as a perfect prediction for PrEP use but rather a guideline for an effective PrEP implementation plan for optimum protection benefit and cost effectiveness. Our models therefore offer an opportunity for modifications which can be achieved by refining the epidemiological assumptions and formulating better assumptions that would improve the model outcomes. The following aspect are some of the important factors that can be considered in improving the predictions in our study.

- Adherence to PrEP drugs varies from one user to another. Incorporation of stochasticity in the models in dealing with variability inherent in any dynamical process is an important aspect to be considered.

- Individuals of different ages may respond differently to PrEP use and reduction of risk behaviour might vary among age groups. Young individuals in the age range [15-30] years are more active in interactions with or between populations than individuals aged between [30-49]. The model would give more insights if an age-structure property is introduced.

- Data on PrEP and ART for improvement and validation of the models outcomes are important steps to be considered. Data fitting provides appropriate values of our model

parameters. Our study did not present any data fitting due to scarcity of data in current PrEP trials.

- Evidence demonstrated that the level of protection of both PrEP drugs (Tenofovir and Truvada) depends on the dose absorbed in the body. Truvada is proven to be more rapidly absorbed than Tenofovir. Tenofovir takes 24 hours while Truvada takes 30 minutes to be absorbed in both vaginal and rectal tissue. Time delay is therefore an important factor to be taken into account. Thus, time dependent delay aspects can be incorporated into our deterministic models for more realistic outcomes.

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